Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated December 18, 2019; last reviewed December 18, 2019)

Key Considerations and Recommendations

- An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster; the two drugs used for this purpose are cobicistat and ritonavir).
- Data also support the use of the two-drug regimen, dolutegravir plus lamivudine, for initial treatment.
- Before initiating antiretroviral therapy (ART) in a person of childbearing potential, a pregnancy test should be performed **(AIII)**. Before prescribing ART to a person of childbearing potential, please refer to Table 6b for information about safety of different INSTI-based regimens taken around the time of conception.
- The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) classifies the following regimens as *Recommended Initial Regimens for Most People with HIV* (in alphabetical order):
  - Bictegravir/tenofovir alafenamide/emtricitabine **(AI)**
  - Dolutegravir/abacavir/lamivudine—**only** for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) coinfection **(AI)**
  - Dolutegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)[a] **(AI)**
  - Dolutegravir/lamivudine **(AI)**—except for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
  - Raltegravir plus (emtricitabine or lamivudine) plus (tenofovir alafenamide [TAF] or tenofovir disoproxil fumarate [TDF])[a] (**BI** for TDF, **BII** for TAF)
- To address individual patient characteristics and needs, the Panel also provides a list of *Recommended Initial Regimens in Certain Clinical Situations* (Table 6a).
- Given the many excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance test results, comorbid conditions, access, and cost. Table 7 provides guidance on choosing an ARV regimen based on selected clinical case scenarios. Table 9 highlights the advantages and disadvantages of different components in a regimen.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

[a] TAF and TDF are two forms of tenofovir that are approved by the Food and Drug Administration. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Introduction

More than 30 antiretroviral (ARV) drugs in seven mechanistic classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. These seven classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), a fusion inhibitor, a CCR5 antagonist, and a CD4 T lymphocyte (CD4) post-attachment inhibitor. In addition, two drugs, ritonavir (RTV) and cobicistat (COBI) are used as pharmacokinetic (PK) enhancers (or boosters) to improve the PK profiles of PIs and the INSTI elvitegravir (EVG).

The initial ARV regimen for a treatment-naive patient generally consists of two NRTIs, usually abacavir/lamivudine (ABC/3TC) or either tenofovir alafenamide/emtricitabine (TAF/FTC) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), plus a drug from one of three drug classes: an INSTI, an NNRTI, or a boosted PI. As shown in clinical trials and by retrospective evaluation of cohorts of patients in clinical care, this strategy for initial treatment has resulted in suppression of HIV replication and CD4 count increases in

most persons with HIV.[1-3] Additional data now support the use of the two-drug regimen dolutegravir (DTG) plus 3TC for initial treatment of people with HIV.[4]

Supporting Evidence and Rationale Used for the Panel's Recommendations

The Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel)'s recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by drug manufacturers for FDA review. In select cases, the Panel considers data from abstracts presented at major scientific meetings. The Panel considers published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates that an ARV regimen produces high rates of viral suppression, increases CD4 count, and has a favorable safety profile to be the strongest evidence on which to base recommendations. Comparative clinical trials of initial treatments generally show no significant differences in HIV-related clinical endpoints or survival. Thus, assessment of regimen efficacy and safety are primarily based on surrogate marker endpoints (especially rates of HIV RNA suppression) and the incidence and severity of adverse events.

In some instances, the Panel recommends regimens that include medications approved by FDA based on bioequivalence or relative bioavailability studies demonstrating that the exposure of the drug(s) in the new formulation or combination is comparable to the exposure of a reference drug(s) that has demonstrated safety and efficacy in randomized clinical trials. When developing recommendations, the Panel may also consider data from randomized switch studies in which a medication in an initial regimen that suppressed patients' viral loads is replaced by a new medication from the same class. Switch trials do not evaluate the ability of a drug or regimen to induce viral suppression; they only examine the drug or regimen's ability to maintain suppression. Therefore, results from switch trials may not be directly applicable to the selection of an initial regimen and should be considered in conjunction with other data, including data from trials conducted in treatment-naive patients and bioequivalence/bioavailability studies. In this section of the guidelines, the definition of an evidence rating of **II** is expanded to include supporting data from bioavailability/bioequivalence studies or randomized switch studies.

When developing recommendations, the Panel also considers tolerability and toxicity profiles, pill burden and dosing frequency, drug interaction potential, cost and access, post-marketing safety data, observational cohort data published in peer-reviewed publications, and the experience of clinicians and community members who are actively engaged in patient care.

The Panel reviewed the available data to arrive at two regimen classifications for ARV-naive patients: (1) *Recommended Initial Regimens for Most People with HIV* and (2) *Recommended Initial Regimens in Certain Clinical Situations* (Table 6a). *Recommended Initial Regimens for Most People with HIV* are those regimens with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use. The Panel also recognizes that, in certain clinical situations, other regimens may be preferred; these options are included in Table 6a in the category of *Recommended Initial Regimens in Certain Clinical Situations*. Examples of clinical scenarios in which certain drugs in these regimens may be particularly advantageous are outlined in Table 7.

There are many other ARV regimens that are effective for initial therapy but have disadvantages when compared with the regimens listed in Table 6a. These disadvantages include greater toxicity, higher pill burden, less supporting data from large comparative clinical trials, or limitations for use in certain patient populations. These other regimens are no longer included in Table 6a. A person with HIV who has a suppressed viral load and is not experiencing any adverse effects while on a regimen that is not listed in Table 6a need not necessarily change to one that is listed in the table. Clinicians should refer to Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further guidance if switching to a new regimen is desired.

Regimens and medications listed in Table 10 below are not recommended as initial therapy. In most instances, a clinician is urged to consider switching a patient who is on one of the regimens listed in Table 10 to a recommended regimen.

In addition to these tables, several tables presented below and at the end of these guidelines provide clinicians with guidance on selecting and prescribing an optimal regimen for an individual patient. Table 9 lists the potential advantages and disadvantages of the different ARV drug components. Appendix B, Tables 3–9 list characteristics of individual ARV agents (e.g., formulations, dosing recommendations, PKs, common adverse effects). Appendix B, Table 10 provides ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Changes Since the Last Revision of the Guidelines

Since the last revision of these guidelines, the Panel has made several important changes to the recommendations for initial therapy in people with HIV. Among these changes, the following deserve emphasis:

- On the basis of 96-week data from the GEMINI-1 and GEMINI-2 trials showing that the efficacy of the two-drug regimen DTG plus 3TC is similar to that of the three-drug regimen DTG plus TDF/FTC,[4] the Panel has added DTG/3TC as one of the regimens *Recommended for Initial Treatment of Most People with HIV* (except for individuals with HIV RNA >500,000 copies/mL, hepatitis B virus (HBV) coinfection, or in whom antiretroviral therapy (ART) is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available).
- In the previous version of these guidelines, because of preliminary data raising concern that DTG use around the time of conception may be associated with an increased risk of infant neural tube defects (NTDs),[5] the Panel recommended against the use of DTG during the first trimester of pregnancy and in those of childbearing potential who are trying to conceive or who are sexually active and not using effective contraception. Now, additional results have shown that the prevalence of infant NTDs in association with DTG exposure at conception is lower than shown in the preliminary data[6,7] but still higher than with non-DTG containing regimens. These updated findings led to revisions in the Panel's recommendation for individuals of childbearing potential. Clinicians should review recommendations in Table 6b before prescribing INSTIs to these patients.
- The Panels' changes to the list of *Recommended Initial Regimens in Certain Clinical Situations* (Table 6a) include the following:
  - Efavirenz (EFV) 400 mg/TDF/3TC has been added based on additional data on the regimen's efficacy **(BI)**.[8]
  - Raltegravir (RAL) plus ABC/3TC and lopinavir/ritonavir (LPV/r) plus 3TC have been removed because other regimens have advantages or more supporting data than these (relatively) less commonly used options.
- Table 7, which outlines clinical situations in which certain medications may be particularly advantageous, has been updated and revised.
- Data from studies showing increased weight gain with particular ARV medications, including some INSTIs and TAF, and especially in certain patient populations (i.e., women, Black people, and Hispanic people), are summarized.
- The section Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal has been updated. DTG/3TC is the preferred regimen because it has the most robust clinical data among the two-drug options in this situation.
- The discussions on clinical trial and safety data in the sections on INSTIs, NRTIs, NNRTIs and PIs have been updated.
- Given the growing number of FDA-approved generic ARV medications, cost and access are increasingly important factors to consider when choosing an ARV regimen (see Cost Considerations and Antiretroviral Therapy).

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy (page 1 of 2)

Selection of a regimen should be individualized based on virologic efficacy, potential adverse effects, childbearing potential and use of effective contraception, pill burden, dosing frequency, drug-drug interaction potential, comorbid conditions, cost, access, and resistance test results. Drug classes and regimens within each class are arranged first by evidence rating, and, when ratings are equal, in alphabetical order. Table 7 provides ARV recommendations based on specific clinical scenarios.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/(TAF or TDF)[a]/FTC **(BI)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c or DRV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- (ATV/c or ATV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC —**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[a]/3TC **(BI)** or DOR plus TAF[a]/FTC **(BIII)**
- EFV plus (TAF or TDF)[a] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)/FTC **(BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC[a] **(CI)**

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

[a] TAF and TDF are two forms of TFV approved by FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy (page 2 of 2)

Note: The following are available as coformulated drugs: ABC/3TC, ATV/c, BIC/TAF/FTC, DOR/TDF/3TC, DRV/c, DRV/c/TAF/FTC, DTG/3TC, DTG/ABC/3TC, EFV (400 mg or 600 mg)/TDF/3TC, EFV/TDF/FTC, EVG/c/TAF/FTC, EVG/c/TDF/FTC, RPV/TAF/FTC, RPV/TDF/FTC, TAF/FTC, TDF/3TC, and TDF/FTC.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TFV = tenofovir; TDF = tenofovir disoproxil fumarate

Table 6b. Considerations Before Initiating Dolutegravir and Other Integrase Strand Transfer Inhibitors as Initial Therapy for Persons of Childbearing Potential

Background:

- Preliminary data from a study in Botswana suggested that there is an increased risk of NTDs (0.9%) in infants born to women who were receiving DTG at the time of conception.[5,9] Updated results have shown that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is lower (0.3%) than reported in the preliminary data, but still higher than in infants who were exposed to ART that did not contain DTG (0.1%).[6,7]
- It is not yet known whether use of other INSTIs around the time of conception also poses a risk of NTDs (i.e., a class effect).
- There are insufficient data to determine whether use of BIC around the time of conception and during pregnancy is safe.
- There is limited data on RAL use around the time of conception. Thus far, based on data collected from the Antiretroviral Pregnancy Registry, the drug manufacturer, and in a cohort study from the United States and other countries, no case of NTD has been reported.[10-12] Among those receiving RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.[10-12]

Before Initiating an INSTI-Containing Regimen in a Person of Childbearing Potential:

- A pregnancy test should be performed **(AIII)**.
- To enable individuals of childbearing potential to make informed decisions, providers should discuss the benefits and risks of using DTG around the time of conception, including the low risk of NTDs and the relative lack of information on the safety of using other commonly prescribed ARV drugs, including other INSTIs, around the time of conception **(AIII)**.
- **For individuals who are trying to conceive,** the Panel recommends initiating one of the following regimens, which are designated as *Preferred* regimens during pregnancy in the Perinatal Guidelines: RAL, ATV/r or DRV/r plus TDF/FTC, TDF/3TC, or ABC/3TC. DTG would be an *Alternative*, rather than a *Preferred*, option **(BII)**.
- **For individuals who are not planning to conceive but who are sexually active and not using contraception**, consider a regimen's effectiveness and tolerability, the available data on potential teratogenicity, and the person's preferences (e.g., low pill burden) when choosing among regimens recommended for initial therapy (Table 6a). In this situation, DTG would be an *Alternative*, rather than *Preferred*, option **(BII)**. If the person becomes pregnant, changes to the ARV regimen may be warranted. Clinicians should refer to the Perinatal Guidelines for recommendations.
- **For individuals who are using effective contraception**, a DTG-based regimen is one of the recommended options; however, clinicians should discuss the risks and benefits of using DTG with patients to allow them to make an informed decision **(AIII)**.
- An approach similar to that outlined for DTG should be considered for BIC-containing ART **(AIII)**.
- EVG/c **should not be used during pregnancy** because of inadequate drug concentrations in the second and third trimesters **(AII)**.
- Clinicians should refer to the Perinatal Guidelines when prescribing ART for a pregnant person with HIV.

***Rating of Recommendations**: A = Strong; B = Moderate; C = Optional*

***Rating of Evidence:** I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion*

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; NTD = neural tube defect; RAL = raltegravir; TDF = tenofovir disoproxil fumarate

Selecting an Initial Antiretroviral Regimen

The goal of ART is to provide a potent, safe, tolerable, and easy-to-adhere-to regimen in order to achieve sustained virologic control. Initial therapy should be with two NRTIs combined with an INSTI, the combination of DTG/3TC or, in some individuals, a combination including two NRTIs plus an NNRTI or an RTV- or COBI-boosted PI. When selecting a regimen for a person with HIV, a number of patient- and regimen-specific characteristics should be considered. Some of the factors can be grouped into the categories listed below and may influence the choice of recommended regimens listed in Table 6a or the decision to consider alternative regimens. Table 7 includes recommendations for additional regimens to use in specific clinical scenarios.

Initial Characteristics to Consider in All Persons with HIV:

- Pretreatment HIV RNA level (viral load)
- Pretreatment CD4 count
- HIV genotypic drug resistance test results. Based on current rates of transmitted drug resistance to different ARV medications, standard genotypic drug-resistance testing in ARV-naive persons should focus on testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted INSTI resistance is a concern, providers should consider also testing for resistance mutations to this class of drugs.
- HLA-B*5701 status. Those who are HLA-B*5701 positive should not receive ABC. Regimens that do not include ABC can be initiated if HLA-B*5701 test results are not yet available; see Table 7 for regimens to initiate.
- Individual preferences
- Anticipated adherence to the regimen
- Timing of ART initiation after diagnosis (i.e., immediate versus delayed)

Note that results of pretreatment HIV RNA, CD4 count, and resistance testing do not need to be available before starting ART. See Table 7 for regimens to initiate if these results are not available.

Presence of Specific Conditions:

- Comorbid conditions: Cardiovascular disease; hyperlipidemia; renal disease; liver disease; osteopenia, osteoporosis, or other conditions associated with bone mineral density (BMD) loss; psychiatric illness; neurologic disease; drug abuse or dependency requiring narcotic replacement therapy
- Pregnancy or potential to become pregnant: Clinicians should refer to Table 6b and the Perinatal Guidelines for more detailed recommendations on the safety and effectiveness of ARV drugs during conception and throughout pregnancy.
- Coinfections: HBV, hepatitis C virus, tuberculosis (TB)

Regimen-Specific Considerations:

- Regimen's barrier to resistance
- Potential adverse effects and drug toxicities, including risk for development of comorbid diseases.
- Known or potential drug interactions with other medications (see Drug-Drug Interactions)
- Convenience (e.g., pill burden, dosing frequency, availability of a fixed-dose combination [FDC] or single-tablet regimen [STR] formulations, food requirements)

- Cost and access (see Cost Considerations and Antiretroviral Therapy)

General Considerations for INSTI-, PI-, or NNRTI-Based Regimens

The choice between an INSTI, PI, or NNRTI in an initial ARV regimen should be guided by the ARV drug's efficacy, barrier to resistance, and adverse effects profile; convenience; the patient's comorbidities and concomitant medications; and the potential for drug-drug interactions (see Tables 7 and 9).

INSTI-Based Regimens

The Panel's *Recommended Initial Regimens for Most People with HIV* as listed in Table 6a include one of three INSTIs (BIC, DTG, or RAL) plus two NRTIs or DTG/3TC. For most patients, these INSTI-containing regimens will be highly effective and have relatively infrequent adverse effects and few drug interactions. In several head-to-head comparisons between boosted PI- and INSTI-containing regimens, the INSTI-based regimens were better tolerated and caused fewer treatment discontinuations.[13-15] The Panel now recommends a two-drug regimen of DTG/3TC for initial therapy if certain criteria are met. Data from two randomized trials showed that, in terms of virologic efficacy, DTG plus 3TC was noninferior to a three-drug regimen of DTG plus TDF/FTC. No treatment-emergent resistance was seen in either the two-drug or the three-drug group. The study inclusion criteria limited enrollment to participants with HIV RNA levels <500,000 copies/mL; no known major NRTI, PI, or NNRTI resistance; and without active hepatitis B.[4,16]

Among the INSTI-based regimens, BIC- and DTG-containing regimens have a higher barrier to resistance and lower pill burden than RAL-containing regimens. However, RAL-containing regimens may be preferred for individuals who wish to become pregnant (see Table 6b for further discussion). Treatment-emergent resistance has been reported very rarely in individuals receiving three-drug DTG-based therapy[17-19] and has not been reported in those receiving BIC-based regimens. In addition, transmitted resistance to BIC and DTG is rare. Because of this high barrier to resistance and tolerability, BIC- and DTG-containing regimens may be considered for patients who plan to start ART before resistance test results are available (e.g., with rapid initiation of ART after diagnosis). BIC-based regimens have been shown to be noninferior to DTG-based regimens in clinical trials.[20,21]

Recent studies have shown that the prevalence of infant NTDs in association with DTG exposure at conception is still higher than with non-DTG containing regimens (0.3% vs. 0.1%, respectively).[6,7] For individuals of childbearing potential who are trying to conceive, DTG would be an *Alternative*, rather than a *Preferred*, option, as recommended in the Perinatal Guidelines. Clinicians should review the revised Table 6b before prescribing ART to a person of childbearing potential.

There are now data suggesting greater weight gain with certain INSTI-based regimens and TAF than with other ARV drugs. The clinical significance of these findings is still unknown.[22-26] EVG-based regimens have the advantage of also being available as STRs and are recommended for certain clinical situations (see Table 7). However, EVG-based regimens have the potential disadvantages of a lower barrier to resistance than DTG- or BIC-containing regimens and, importantly, a greater potential for drug interactions because EVG is combined with COBI, a strong cytochrome P (CYP) 3A4 inhibitor.

Protease Inhibitor-Based Regimens

PK-enhanced PI-based regimens are recommended in certain clinical situations. Similar to elvitegravir/cobicistat (EVG/c), they carry the disadvantage of greater drug interaction potential than other ARV drugs. For those individuals in whom ART needs to begin urgently before resistance test results are available, boosted DRV may be an appropriate choice because the rate of transmitted PI resistance is low and boosted DRV has a high barrier to resistance and a low rate of treatment-emergent resistance. DRV/c/TAF/FTC is available as an STR. Boosted ATV, like boosted DRV, has relatively few metabolic adverse effects in comparison to older boosted-PI regimens; however, ATV/r had a higher rate of adverse effect-associated drug discontinuation than darunavir/ritonavir (DRV/r) or RAL in a randomized clinical trial.[13] In a substudy of this

trial, and in a separate cohort study, atazanavir/ritonavir (ATV/r) use was associated with slower progression of atherosclerosis, as measured by carotid artery intima medial thickness.[27,28] Large observational cohorts found an association between some PIs (DRV/r, fosamprenavir [FPV], indinavir [IDV], and LPV/r) and an increased risk of cardiovascular events; however, this association was not seen with ATV.[29-34] Further study is needed.

NNRTI-Based Regimens

NNRTI-based regimens (which include doravirine [DOR], EFV, or rilpivirine [RPV]) may be options for some patients, although these drugs, especially EFV and RPV, have low barriers to resistance. The emergence of resistance at the time of virologic failure has also been reported with DOR. EFV has a long track record of widespread use, is considered safe in persons of childbearing potential, and has minimal PK interaction with rifamycins, making it an attractive option for patients who require TB treatment. EFV-based regimens (using either 400 mg or 600 mg dosing) have excellent virologic efficacy,[35] including in patients with high HIV RNA (except when EFV is used with ABC/3TC); however, the relatively high rate of central nervous system (CNS)-related side effects reduces the tolerability of EFV-based regimens. As an STR, EFV 600 mg is available with TDF/FTC or TDF/3TC; EFV 400 mg is available with TDF/3TC. RPV has fewer adverse effects than EFV, is available as one of the smallest tablet sizes among STRs that also include TAF/FTC or TDF/FTC, and has a favorable lipid profile. However, RPV has lower virologic efficacy in patients with baseline HIV RNA levels >100,000 copies/mL and CD4 counts <200 cells/mm^3. DOR is available both as a single-drug tablet to be used with two NRTIs and as part of an STR with TDF/3TC. In randomized trials, DOR was noninferior to both EFV and DRV/r when either of these drugs were taken in combination with two NRTIs.[36,37] DOR has CNS tolerability advantages over EFV and more favorable lipid effects than DRV/r and EFV. DOR also has fewer potential drug interactions than EFV or RPV, and unlike with RPV, the virologic efficacy of DOR is not compromised in patients with high HIV RNA levels and low CD4 counts.

Regimens When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

In those patients in whom ABC, TDF, or TAF cannot be used or are not optimal, there are several two-drug options that do not contain these agents. Two-drug options **should not be used** in individuals with HBV coinfection or known pre-existing resistance to either ARV in the combination. Among the two-drug regimens, DTG/3TC is preferred because there are substantial data for this combination in initial therapy, with the caveat that people with HIV RNA >500,000 copies/mL were excluded from the largest trial.[4,16] Another two-drug treatment option that can be considered is the combination of DRV/r (once daily) plus RAL (twice daily), but this combination should only be used in those with baseline CD4 counts >200 cells/mm^3 and HIV RNA levels <100,000 copies/mL.[38] A small, randomized trial indicated that once-daily DRV/r plus 3TC had similar efficacy to once-daily DRV/r plus TDF/3TC, although this study has yet to be published.[39]

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 1 of 4)

This table guides clinicians in choosing an initial ARV regimen according to various patient and regimen characteristics and specific clinical scenarios. When more than one scenario applies to a person with HIV, clinicians should review considerations for each relevant scenario and use their clinical judgment to select the most appropriate regimen. This table is intended to guide the initial choice of regimen. However, if a person is doing well on a particular regimen, it is not necessary to switch to another regimen based on the scenarios outlined in this table. Please see Table 9 for additional information regarding the advantages and disadvantages of particular ARV medications. **Before initiating an INSTI-based regimen in a person of childbearing potential, review Table 6b for considerations in choosing the regimen.**

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Pre-ART Characteristics	CD4 count <200 cells/mm^3	**Do Not Use the Following Regimens:** • RPV-based regimens • DRV/r plus RAL	A higher rate of virologic failure has been observed in those with low pretreatment CD4 counts.
	HIV RNA >100,000 copies/mL (also see next row if HIV RNA >500,000 copies/mL)	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL	Higher rates of virologic failure have been observed in those with high pretreatment HIV RNA levels
	HIV RNA >500,000 copies/mL	**Do Not Use the Following Regimens:** • RPV-based regimens • ABC/3TC with EFV or ATV/r • DRV/r plus RAL • DTG/3TC	For DTG/3TC, limited data are available in patients above this viral load threshold.
	HLA-B*5701 positive or result unknown	**Do not use ABC-containing regimens.**	ABC hypersensitivity, a potentially fatal reaction, is highly associated with the presence of the HLA-B*5701 allele.
	ARV should be started before HIV drug resistance results are available (e.g., in a person with acute HIV) or when ART is being initiated rapidly.	**Avoid NNRTI-based regimens and DTG/3TC.** **Avoid ABC.** **Recommended ART Regimens:** • BIC/TAF/FTC • DTG plus (TAF or TDF)[a] plus (3TC or FTC) • (DRV/r or DRV/c) plus (TAF or TDF)[a] plus (3TC or FTC)	Transmitted mutations conferring NNRTI and NRTI resistance are more likely than mutations associated with PI or INSTI resistance. HLA-B*5701 results may not be available rapidly. Transmitted resistance to DRV, BIC, and DTG is rare, and these drugs have high barriers to resistance.
ART-Specific Characteristics	A one-pill, once-daily regimen is desired	**STR Options as Initial ART Include:** • BIC/TAF/FTC • DOR/TDF/3TC • DRV/c/TAF/FTC • DTG/ABC/3TC • DTG/3TC • EFV/TDF/FTC • EFV/TDF/3TC • EVG/c/TAF/FTC • EVG/c/TDF/FTC • RPV/TAF/FTC • RPV/TDF/FTC	Do not use DTG/ABC/3TC if patient is HLA-B*5701 positive. DTG/3TC **is not recommended** if HIV RNA is >500,000 copies/mL. Do not use DTG/ABC/3TC or DTG/3TC in the setting of HBV coinfection or unknown HBV status. Do not use RPV-based regimens if HIV RNA is >100,000 copies/mL and CD4 count is <200/mm^3. See Appendix B, Table 10 for ARV dose recommendations in the setting of renal impairment.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 2 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
ART-Specific Characteristics, continued	Food effects	**Regimens that Can be Taken Without Regard to Food:** • BIC-, DOR-, DTG-, or RAL-based regimens	Oral bioavailability of these regimens is not significantly affected by food.
		Regimens that Should be Taken with Food: • ATV/r- or ATV/c-based regimens • DRV/r- or DRV/c-based regimens • EVG/c/TAF/FTC[a] • EVG/c/TDF/FTC[a] • RPV-based regimens	Food improves absorption of these regimens. RPV-containing regimens should be taken with ≥390 calories of food.
		Regimens that Should be Taken on an Empty Stomach: • EFV-based regimens	Food increases EFV absorption and may increase CNS side effects.
Presence of Other Conditions	Chronic kidney disease (defined as CrCl <60 mL/min)	**In general, avoid TDF.** ABC may be used if patient is HLA-B*5701 negative. If HIV RNA is >100,000 copies/mL, do not use ABC/3TC plus (EFV or ATV/r). TAF may be used if CrCl >30 mL/min or if patient is on chronic hemodialysis (only studied with EVG/c/TAF/FTC). Consider avoiding ATV. **ART Options When ABC, TAF, or TDF Cannot be Used:** • DTG/3TC (if HIV RNA <500,000 copies/mL and without HBV coinfection) • DRV/r plus 3TC • DRV/r plus RAL (if CD4 count >200 cells/mm^3 and HIV RNA <100,000 copies/mL)	TDF has been associated with proximal renal tubulopathy. Higher rates of renal dysfunction have been reported in patients using TDF in conjunction with RTV-containing regimens. An adjusted dose of TDF can be used in patients with ESRD or in those who are on hemodialysis. Refer to Appendix B, Table 10 for specific dosing recommendations. TAF has less impact on renal function and lower rates of proteinuria than TDF. ATV has been associated with chronic kidney disease in some observational studies. ABC has not been associated with renal dysfunction.
	Liver disease with cirrhosis	Some ARVs are contraindicated or may require dosage modification in patients with Child-Pugh class B or C disease.	Refer to Appendix B, Table 10 for specific dosing recommendations. Patients with cirrhosis should be carefully evaluated by an expert in advanced liver disease.
	Osteoporosis	**Avoid TDF.**[a] ABC may be used if patient is HLA-B*5701 negative. If HIV RNA is >100,000 copies/mL, **do not use** ABC/3TC plus (EFV or ATV/r).	TDF is associated with decreases in BMD along with renal tubulopathy, urine phosphate wasting, and resultant osteomalacia. TAF[a] and ABC are associated with smaller declines in BMD than TDF.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 3 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Psychiatric illnesses	**Consider avoiding EFV- and RPV-based regimens.** Patients on INSTI-based regimens who have pre-existing psychiatric conditions should be closely monitored. Some ARVs are contraindicated, and some psychiatric medications need dose adjustments when coadministered with certain ARVs.	EFV and RPV can exacerbate psychiatric symptoms and may be associated with suicidality. INSTIs have been associated with adverse neuropsychiatric effects in some retrospective cohort studies and case series. See the drug-drug interaction tables (Tables 21a, 21b, and 21d) for dosing recommendations when drugs used for psychiatric illnesses are used with certain ARVs.
	HIV-associated dementia (HAD)	**Avoid EFV-based regimens if possible.**	The beneficial effects of ART on HAD-symptoms may be confounded by EFV-related neuropsychiatric effects.
	Medication-assisted treatment for opioid use disorder	Opioid withdrawal may occur when EFV is initiated in patients who are on a stable dose of methadone. Clinical monitoring is recommended, as medications used to treat opioid dependence may need to be adjusted in some patients.	EFV reduces methadone concentrations and may lead to withdrawal symptoms. See the drug-drug interaction tables (Tables 21a, 21b, and 21d) for dosing recommendations.
	Cardiac QTc interval prolongation	Consider avoiding EFV- or RPV-based regimens if patient is taking other medications with known risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.	High EFV or RPV concentrations may cause QT prolongation.
	High cardiac risk	Consider avoiding ABC- and LPV/r -based regimens. If a boosted PI is the desired option, an ATV-based regimen may have advantages over a DRV-based regimen. Refer to Hyperlipidemia below for regimens associated with more favorable lipid profiles.	An increased risk of CV events with ABC has been observed in some studies. Observational cohort studies reported an association between some PIs (DRV, IDV, FPV, and LPV/r) and an increased risk of CV events; this risk has not been seen with ATV (see text). Further study is needed. Certain ART regimens are associated with more favorable lipid profiles than other regimens, although evidence on whether this improves CV outcomes is lacking.
	Hyperlipidemia	**The Following ARV Drugs Have Been Associated with Dyslipidemia:** • PI/r or PI/c • EFV • EVG/c BIC, DOR, DTG, RAL, and RPV have fewer lipid effects. TDF lowers lipids; therefore, switching from TDF to TAF is associated with increased lipids.	TDF has been associated with lower lipid levels than ABC or TAF.

Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios (page 4 of 4)

Patient or Regimen Characteristics	Clinical Scenario	Consideration(s)	Rationale/Comments
Presence of Other Conditions, continued	Patients with history of poor adherence to non-ARV medications or inconsistent engagement in care	Consider using regimens with a boosted PI or BIC or DTG.	These regimens have a high genetic barrier to resistance.
	Pregnancy	Refer to Table 6b and the Perinatal Guidelines for further guidance on ARV use during pregnancy.	
	Patients of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception	Refer to Table 6b for further guidance.	
Presence of Coinfections	HBV infection	Use TDF or TAF, with FTC or 3TC **If TDF and TAF Are Contraindicated:** • For treatment of HBV, use FTC or 3TC with entecavir and a suppressive ART regimen (see HBV/HIV Coinfection).	TDF, TAF, FTC, and 3TC are active against both HIV and HBV. 3TC- or FTC-associated HBV mutations can emerge rapidly when these drugs are used without another drug that is active against HBV.
	HCV treatment required	Refer to recommendations in HCV/HIV Coinfection, with special attention to potential interactions between ARV drugs and HCV drugs.	
	Treating TB disease with rifamycin antibiotics (rifabutin, rifampin, and rifapentine)	Recommended regimens may require dose adjustment. See the drug-drug interaction tables (Tables 21a-e) and TB/HIV Coinfection for information on ARV use with rifamycin antibiotics.	Rifamycin antibiotics are inducers of CYP3A4 and UGT1A1 enzymes, causing significant decreases in concentrations of PIs, INSTIs, and RPV.

[a] TAF and TDF are two FDA-approved forms of TFV. TAF has fewer bone and kidney toxicities than TDF, whereas TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BID = twice daily; BMD = bone mineral density; COBI = cobicistat; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ESRD = end stage renal disease; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FPV = fosamprenavir; FTC = emtricitabine; HAD = HIV-associated dementia; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; STR = single-tablet regimen; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; UGT = uridine diphosphate glucuronosyltransferase

Characteristics of Antiretroviral Drugs Recommended for Initial Therapy

The following sections provide detailed information on ARV drugs that the Panel recommends for initial therapy for persons with HIV, including the drugs' characteristics and adverse effects profiles, results from related clinical trials, and Panel recommendations on their use.

Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy

Table 8a. Characteristics of Nucleoside Reverse Transcriptase Inhibitor Options Recommended for Antiretroviral Therapy-Naive Patients

<table>
<tr><th>Characteristics</th><th>ABC/3TC</th><th>3TC[a]</th><th>TDF/3TC</th><th>TAF/FTC</th><th>TDF/FTC</th></tr>
<tr><td>Dosing Frequency</td><td>Once daily</td><td>Once daily</td><td>Once daily</td><td>Once daily</td><td>Once daily</td></tr>
<tr><td>Available Coformulations for ART-Naive Patients</td><td>• ABC/3TC
• DTG/ABC/3TC</td><td>DTG/3TC</td><td>• TDF/3TC
• DOR/TDF/3TC
• EFV 600 mg/TDF/3TC
• EFV 400 mg/TDF/3TC</td><td>• TAF 25 mg/FTC
• BIC/TAF 25 mg/FTC
• DRV/c/TAF 10 mg/FTC
• EVG/c/TAF 10 mg/FTC
• RPV/TAF 25 mg/FTC</td><td>• TDF/FTC
• EFV/TDF/FTC
• EVG/c/TDF/FTC
• RPV/TDF/FTC</td></tr>
<tr><td rowspan="2">Adverse Effects</td><td>ABC:
• HSR to ABC is associated with the presence of HLA-B*5701 allele.
• Increase in CV events is associated with ABC use in some, but not all, cohort studies.</td><td>See below</td><td>TDF:
• Renal insufficiency, proximal renal tubulopathy
• Decrease in BMD
• Renal and bone toxicity are exacerbated by pharmacologic boosters.</td><td>TAF:
• Renal insufficiency, proximal renal tubulopathy (less frequent than with TDF)
• Decrease in BMD (less than with TDF; similar to with ABC)</td><td>TDF:
• Renal insufficiency, proximal renal tubulopathy
• Decrease in BMD
• Renal and bone toxicity are exacerbated by pharmacologic boosters.</td></tr>
<tr><td colspan="3">3TC: No significant adverse effects</td><td colspan="2">FTC: Skin discoloration</td></tr>
<tr><td rowspan="2">Other Considerations</td><td colspan="3">ABC:
• Perform HLA-B*5701 testing before initiating ABC; if result is positive, do not start ABC and add ABC to patient's allergy list.
3TC:
• Epivir HBV™ is for the treatment of HBV and contains a different dose of 3TC than the formulation for ART. Thus, Epivir HBV™ should not be used for HIV treatment.
• Coadministration of 3TC with sorbitol-containing drugs decreases 3TC concentration and should be avoided.</td><td colspan="2">FTC should not be used as sole treatment for HBV due to development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.</td></tr>
<tr><td colspan="2">3TC or ABC/3TC should not be used as treatment for HBV due to development of resistance. Discontinuation may precipitate HBV flare if no other agents active against HBV are present.</td><td colspan="2">Also used for HBV treatment. Discontinuation may precipitate HBV flare.
See Appendix B, Table 10 for dose recommendations in patients with renal insufficiency.</td></tr>
</table>

[a] 3TC is recommended for use with DTG in ART-naive persons, and with DRV/r if ABC, TDF, and TAF are not optimal. Otherwise, dual-NRTI backbones are recommended.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; BIC = bictegravir; BMD = bone mineral density; CV = cardiovascular; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

FDA-approved NRTIs include zidovudine (ZDV), stavudine (d4T), didanosine (ddI), ABC, TDF, TAF, 3TC, and FTC. Older NRTIs (ZDV, d4T, ddI) are no longer recommended for use in clinical practice in the United States because of high rates of serious toxicities, including peripheral neuropathy and mitochondrial toxicity that may lead to myopathy, hepatic steatosis, lactic acidosis, lipoatrophy, and bone marrow suppression from ZDV use. The incidence of these complications is much lower with 3TC, FTC, ABC, TDF, and TAF than with older NRTIs.[40,41]

ABC/3TC, TAF/FTC, TDF/3TC, and TDF/FTC are NRTI combinations that are recommended as components of initial therapy. In addition, 3TC may be used as a single NRTI with DTG, or, in select circumstances, with boosted DRV. Table 6a provides recommendations and ratings for the individual regimens. These recommendations are based on the virologic potency and durability, short- and long-term toxicity, and dosing convenience of these drugs. TDF has been associated with bone and kidney toxicities, especially when used with a pharmacologic booster.[42] TAF is less likely to cause kidney and bone toxicities than TDF. TDF is associated with lower lipid levels than TAF. Safety, cost, and access are among the factors to consider when choosing between these drugs. ABC/3TC, TDF/3TC, and 3TC are available as generic formulations.

Clinical Trials Comparing Nucleoside Reverse Transcriptase Inhibitors

Abacavir/Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

Several randomized controlled trials in ART-naive participants compared ABC/3TC to TDF/FTC, each administered in combination with a third ARV drug[43-45] (see also the discussion in the Dolutegravir section).[46]

- The ACTG 5202 study, a randomized controlled trial in >1,800 participants, evaluated the efficacy and safety of ABC/3TC and TDF/FTC when each combination was used with either EFV or ATV/r. In patients with baseline HIV RNA ≥100,00 copies/mL, the time to virologic failure was significantly shorter with ABC/3TC than with TDF/FTC, regardless of whether the third active drug was EFV or ATV/r.[43] In the HEAT study, 688 participants received ABC/3TC or TDF/FTC in with once-daily LPV/r. Virologic efficacy was similar in the two study arms, including in a subgroup of participants with HIV RNA ≥100,000 copies/mL.[45]
- The ASSERT study compared open-label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative, ART-naive patients; all participants also received EFV. The primary study endpoint was renal safety of the regimens. At week 48, the proportion of participants with HIV RNA <50 copies/mL was lower among ABC/3TC-treated participants than among TDF/FTC-treated participants.[44]

Lamivudine Compared to Tenofovir Disoproxil Fumarate/Emtricitabine

An STR of DTG/3TC has now been approved as an initial ART regimen. Please refer to the INSTI section for full discussion.

GEMINI 1 and GEMINI 2 were identically designed randomized, double-blind clinical trials that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naive adults with HIV RNA <500,000 copies/mL and estimated glomerular filtration rate (eGFR) ≥50 mL/min.[4,16]

Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate

- Two randomized double-blind Phase 3 clinical trials compared the safety and efficacy of EVG/c/TDF/FTC and EVG/c/TAF/FTC in 1,733 ART-naive adults with eGFR ≥50 mL/min.
  - TAF/FTC was virologically noninferior to TDF/FTC at week 48 (92% vs. 90% of participants had plasma HIV RNA <50 copies/mL, respectively),[47] but TAF/FTC was superior to TDF/FTC at week 144 (84.2% vs. 80% of participants with plasma HIV RNA <50 copies/mL), largely driven by a

higher rate of treatment discontinuation in the TDF arm.[48]

- Participants in the TAF arm had significantly smaller reductions in BMD at the spine and hip than those in the TDF arm through 144 weeks.[48] Those receiving TAF also had less pronounced changes in eGFR and renal biomarkers and fewer clinically significant renal events through week 96.[49] Conversely, levels of fasting low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides increased more in the TAF group than in the TDF group at 96 weeks, with no change in total cholesterol to HDL ratio.[50]

- Two randomized studies have compared the safety and efficacy of TAF/FTC to TDF/FTC each combination administered with boosted DRV in ART-naive participants:
  - A Phase 2 study of coformulated darunavir/cobicistat (DRV/c) plus TAF/FTC versus DRV/c plus TDF/FTC in treatment-naive patients demonstrated similar virologic suppression rates in both arms (75% vs. 74%).[51] In the TAF arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among participants in the TAF group.
  - The AMBER study randomized ART-naive participants to receive either coformulated DRV/c/TAF/FTC or DRV/c plus TDF/FTC. At 48 weeks, HIV RNA <50 copies/mL was achieved in 91% of the DRV/c/TAF/FTC participants versus 88% of the DRV/c plus TDF/FTC participants. Participants in the TAF/FTC arm showed less decline in hip and spine BMD and eGFR than participants in the TDF/FTC arm.[52]

- One analysis evaluated data from 11 randomized trials that compared the virologic efficacy, frequency of renal events, and bone density changes associated with the use of TDF and of TAF when either drug was taken with or without PK boosters (RTV or COBI). There were no significant differences between unboosted TDF and TAF in terms of virologic efficacy or in the number of participants who discontinued treatment because of renal or bone adverse events or fractures. However, bone- and renal-related toxicities were more pronounced when TDF was used with RTV or COBI.[42]
- To assess the ability of TAF to maintain HIV and HBV suppression, 72 patients with HIV/HBV coinfection who had HIV RNA <50 copies/mL and HBV DNA <9 $\log_{10}$ IU/mL on a stable regimen were switched to EVG/c/TAF/FTC.[53] In this study, 96% of participants were on a TDF/FTC-containing regimen before the switch. Key results of the study showed that:
  - Among those who switched to EVG/c/TAF/FTC, HIV suppression was maintained in 94.4% and 91.7% of participants at 24 and 48 weeks, respectively. At 24 and 48 weeks, 86.1% and 91.7% of participants, respectively, had HBV DNA <29 $\log_{10}$ IU/mL.
  - Markers of proximal tubular proteinuria and biomarkers of bone turnover decreased in those who switched to EVG/c/TAF/FTC.[53]

Nucleoside Reverse Transcriptase Inhibitor Options for Initial Therapy

In alphabetical order.

Abacavir/Lamivudine (ABC/3TC)

ABC plus 3TC has been studied in combination with EFV, several PIs, and DTG in ART-naive patients.[46,54-56]

Adverse Effects

Hypersensitivity Reactions:

- Clinically suspected hypersensitivity reactions (HSRs) were observed in 5% to 8% of individuals who started ABC in clinical trials conducted before the use of HLA-B*5701 testing. The risk of HSRs is highly associated with the presence of the HLA-B*5701 allele; approximately 50% of HLA-B*5701-positive patients, if given ABC, will have a related HSR.[57,58] HLA-B*5701 testing should be done if the

use of ABC is being considered. A patient who tests positive for HLA-B*5701 should not be given ABC and ABC hypersensitivity should be noted on the patient's allergy list. Patients who are HLA-B*5701 negative are far less likely to experience an HSR, but they should be counseled about the symptoms of the reaction. Patients who discontinue ABC because of a suspected HSR **should never be rechallenged**, regardless of their HLA-B*5701 status.

Cardiovascular Risk:

- An association between ABC use and myocardial infarction (MI) was first reported in the D:A:D study. This large, multinational, observational study group found that recent (i.e., within 6 months) or current use of ABC was associated with an increased risk of an MI, particularly in participants with pre-existing cardiac risk factors.[30,59]
- Since the D:A:D report, several studies have evaluated the relationship between ABC therapy and cardiovascular events. Some studies have found an association.[60-66] Others, including an FDA meta-analysis of 26 randomized clinical trials that evaluated ABC, have not.[29,67-70]
- An analysis of data from NA-ACCORD found that use of ABC in the previous 6 months was associated with an increased risk of both type 1 and type 2 MIs after adjusting for cardiovascular disease risk factors.[71]
- No consensus has been reached on the association between ABC use and MI risk or the mechanism for such an association.

Other Factors and Considerations:

- ABC/3TC is available as a coformulated tablet and as a coformulated STR with DTG.
- ABC and 3TC are available separately and as a coformulated tablet in generic tablet formulations.
- ABC does not cause renal dysfunction and can be used instead of TDF in patients with underlying renal dysfunction or in those who are at high risk for renal effects. No dose adjustment is required in patients with renal dysfunction.

The Panel's Recommendations:

- ABC should only be prescribed for patients who are HLA-B*5701 negative.
- On the basis of clinical trial safety and efficacy data, experience in clinical practice, and the availability of DTG/ABC/3TC as an FDC, the Panel classifies DTG/ABC/3TC as a *Recommended Initial Regimen for Most People with HIV* **(AI)** (see the discussion of DTG in this section regarding the clinical efficacy data for ABC/3TC plus DTG).
- ABC/3TC use with EFV, ATV/r, atazanavir/cobicistat (ATV/c), DRV/c, DRV/r, or RAL is only recommended for patients with pretreatment HIV RNA levels <100,000 copies/mL. See Table 6a for more detailed recommendations on the use of ABC/3TC with these drugs.
- ABC should be used with caution or avoided in patients with known high cardiovascular risk.

Lamivudine (3TC) as Single NRTI

3TC was approved for HIV treatment in 1995 and is often used in combination with ABC or TDF. Based on the GEMINI-1 and GEMINI-2 studies[4] that found DTG plus 3TC noninferior to DTG plus TDF/FTC in ART-naive patients with HIV RNA <500,000 copies/mL, 3TC may be used as a single NRTI with DTG (for more information, please refer to INSTI section). In addition, based on the ANDES trial, if ABC, TDF, and TAF cannot be used, 3TC can be used as a single NRTI with DRV/r[39] (please refer to Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate

Cannot Be Used or Are Not Optimal.)

Adverse Effects:

- Long-term experience with 3TC has shown that it is well tolerated with no significant adverse effects.

Other Factors and Considerations:

- 3TC is available as an STR with DTG.
- 3TC has activity against HBV but is insufficient for HBV treatment when used alone due to the emergence of resistance. Discontinuation of 3TC can precipitate a flare in HBV if no other HBV-active drugs are in the regimen.
- There are two brand-name formulations of 3TC (one for HIV and the other for HBV), but doses are different. The dose for HIV treatment is 3TC 300 mg daily.
- The dose of 3TC should be adjusted in patients with creatinine clearance (CrCl) <50 mL/min.
- Sorbitol-containing drugs can decrease 3TC concentration and co-administration should be avoided.

The Panel's Recommendations:

- The Panel recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People with HIV* with three exceptions. DTC/3TC **is not recommended** for:
  - Individuals with HIV RNA >500,000 copies/mL;
  - Individuals with HBV coinfection or whose HBV status is unknown; *and*
  - Individuals starting ART before the results of genotypic resistance testing for reverse transcriptase are available.

Tenofovir Alafenamide/Emtricitabine (TAF/FTC)

TAF, an oral prodrug of tenofovir (TFV), is hydrolyzed to TFV in plasma and then converted to TFV-diphosphate (TFV-DP) intracellularly, where it exerts its activity as an NRTI. Unlike TDF, which readily converts to TFV in plasma after oral absorption, TAF remains relatively stable in plasma, resulting in lower plasma and higher intracellular TFV concentrations. After oral administration, TAF 25 mg resulted in plasma TFV concentrations that were 90% lower than those seen with TDF 300 mg. Intracellular TFV-DP concentrations, however, were substantially higher with TAF.

Adverse Effects

Renal and Bone Effects:

- The potential for adverse kidney and bone effects is lower with TAF than with TDF. In randomized controlled trials that compared TAF and TDF in treatment-naive or virologically suppressed patients, TAF had more favorable effects on renal biomarkers and bone density than TDF (described below).

Lipid Effects:

- In randomized controlled trials in ART-naive patients, as well as in switch studies (described below), levels of LDL and HDL cholesterol and triglycerides were higher in patients receiving TAF than in patients receiving TDF. However, total cholesterol to HDL ratios did not differ between patients receiving TAF and those receiving TDF. The clinical significance of this finding is not clear.[47,72,73]

Weight Gain:

- Initiation of TAF in ART-naive individuals has been associated with greater weight gain than initiation of TDF[23,24] and ABC.[23] Significant weight gain was initially reported in a cohort of patients switching from TDF-containing to TAF-containing regimens.[74] In ADVANCE, an open-label trial conducted in

South Africa that compared EFV/TDF/FTC versus DTG plus TDF/FTC versus DTG plus TAF/FTC in ART-naive patients, there was a greater increase in body weight with initiation of TAF than with TDF.[24] Weight gain was most pronounced in black women (10 kg over 96 weeks). This is an area of intense investigation and the clinical significance of the effect is still uncertain. It is also unclear whether change of therapy results in reversal of weight gain.

Other Factors and Considerations:

- TAF/FTC is available in FDCs with bictegravir (BIC), DRV/c, EVG/c, or RPV, allowing the regimens to be administered as a single pill taken once daily with food.
- In Phase 3 randomized trials, BIC/TAF/FTC was comparable to DTG/ABC/3TC and to DTG plus TAF/FTC (see the INSTI section below).
- TAF-containing regimens are approved for patients with eGFR ≥30 mL/min. Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TAF, and these assessments should be repeated periodically during treatment. EVG/c/FTC/TAF was safe and effective in a single-arm switch study that was conducted in patients on hemodialysis with eGFR <15 mL/min.[75]
- Both TAF and FTC are active against HBV. In patients with HIV/HBV coinfection, TAF/FTC may be used as the NRTI pair in an ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).[53]

The Panel's Recommendation:

- On the basis of clinical trial safety and efficacy data, supportive bioequivalence data,[76] and its availability as a component of various FDCs, the Panel considers TAF/FTC a recommended NRTI combination for initial ART in most persons with HIV when prescribed with BIC, DTG, and RAL.

Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) and Tenofovir Disoproxil Fumarate/Lamivudine (TDF/3TC)

TDF, with either 3TC or FTC, has been studied in combination with DOR, EFV, RPV, several boosted PIs, EVG/c, RAL, and DTG in randomized clinical trials.[77-86] In a 10-day, open-label, randomized, monotherapy trial that was not powered to find a difference between study arms, the reduction in viral load from baseline was 1.7 $\log_{10}$ for FTC 200 mg once daily and 1.5 $\log_{10}$ for 3TC 150 mg twice daily.[87] In a meta-analysis of 12 trials, there was no significant difference in treatment success between 3TC and FTC.[88] In the ATHENA cohort, virologic efficacy of TDF/FTC was compared to TDF/3TC when either was combined with an NNRTI (EFV or nevirapine [NVP])[89] or with a boosted PI.[90] TDF/3TC was associated with higher rates of virologic failure than TDF/FTC in the NNRTI analysis. However, it is noteworthy that the participants in the NNRTI cohort who were taking 3TC generally had higher viral loads, lower CD4 counts, and were more likely to be using injection drugs at the start of the study than those taking FTC.[89] There was no difference in the rates of virologic failure in people who were taking TDF/FTC and people who were taking TDF/3TC when these drug combinations were used with a boosted PI.[90] A retrospective analysis of an Italian national database found that viral resistance was more common with TDF/3TC than with TDF/FTC, but this was not observed in clinical trials.[91]

Adverse Effects

Renal Effects:

- New onset or worsening renal impairment has been associated with TDF use.[92,93] Risk factors may include advanced HIV disease, longer treatment history, low body weight (especially in women),[94] and pre-existing renal impairment.[95] Concomitant use of a PK-enhanced regimen (with a PI or EVG) can increase TDF concentrations; studies have suggested that the risk of renal dysfunction is greater when TDF is used in these regimens. As previously noted, adverse effects on renal biomarkers such as

proteinuria, especially tubular proteinuria, were more frequent with TDF than with TAF.[93,95-99]

- Adverse renal outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that discontinuation due to renal adverse events is more frequent in people who take TDF/FTC with PK boosting.[42]

Bone Effects:

- While initiation of all NRTI-containing regimens has been associated with a decrease in BMD, the loss of BMD is greater with TDF-containing regimens. For example, in two randomized studies that compared TDF/FTC with ABC/3TC, participants who received TDF/FTC experienced a significantly greater decline in BMD than ABC/3TC-treated participants.[100,101] BMD generally stabilizes following an early decline after ART initiation. Loss of BMD with TDF is also greater than with TAF (see above).
- Cases of osteomalacia associated with proximal renal tubulopathy have been reported with the use of TDF.[102]
- Adverse bone outcomes are more likely when TDF/FTC is coadministered with PK boosters (RTV or COBI). A meta-analysis of randomized trials found that fractures and study discontinuations due to bone adverse events occured more frequently among patients who took TDF/FTC with PK boosting than among those who took TAF/FTC with PK boosting.[42]

Other Factors and Considerations:

- TDF/FTC is available in FDCs with EFV, EVG/c, and RPV, allowing the regimens to be administered as a single pill taken once daily.
- TDF/3TC is available in FDCs with DOR 100 mg, EFV 600 mg, and EFV 400 mg.
- Renal function, urine glucose, and urine protein should be assessed before initiating treatment with TDF and periodically during treatment (see Laboratory Testing for Initial Assessment and Monitoring). In patients who have pre-existing renal insufficiency (CrCl <60 mL/min),[103] use of TDF should generally be avoided. If TDF is used, a dose adjustment is required if the patient's CrCl falls below 50 mL/min (see Appendix B, Table 10 for dose recommendations).
- TDF, FTC, and 3TC are active against HBV. In patients with HBV/HIV coinfection, TDF/FTC or TDF/3TC may be used as the NRTI pair of the ART regimen because these drugs have activity against both viruses (see HBV/HIV Coinfection).

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, long-term experience in clinical practice, and the combination's availability as a component of FDC drugs, the Panel considers TDF/FTC and TDF/3TC as recommended NRTI combinations for initial ART in most persons with HIV when combined with DTG or RAL. See Table 6a for recommendations regarding use of TDF/FTC with other drugs.
- TDF should be used with caution or avoided in patients with renal disease and osteoporosis.
- When TDF is used, especially in conjunction with a PK booster, clinicians should monitor for renal and bone safety during therapy. Boosters should be avoided when possible in patients taking TDF.

Integrase Strand Transfer Inhibitor–Based Regimens

Table 8b. Characteristics of Integrase Strand Transfer Inhibitors That Are Recommended for Antiretroviral Therapy-Naive Patients

Before starting an INSTI-based regimen in a person of childbearing potential, clinicians should refer to Table 6b for further guidance.

Characteristics	BIC	DTG	EVG	RAL
Dosing Frequency	Once daily	**Once Daily:** • In ART-naive or INSTI-naive persons **Twice Daily:** • If used with certain CYP3A4 and UGT1A1 inducers; *or* • In INSTI-experienced persons with certain INSTI drug resistance mutations	Once daily; requires boosting with COBI	• 400 mg twice daily, *or* • 1,200 mg (two 600-mg tablets) once daily
STR Available for ART-Naive Patients	BIC/TAF/FTC	• DTG/ABC/3TC • DTG/3TC	• EVG/c/TAF/FTC • EVG/c/TDF/FTC	No
Available as a Single-Drug Tablet	No	Yes	No	Yes
Approved for ART-Experienced Patients	No	Yes, with twice-daily dosing for patients with certain INSTI drug resistance mutations	No, but sometimes used in combination with DRV and TAF/FTC as part of a simplification regimen in patients with resistance.	Yes, for patients with drug resistance mutations to RTV-boosted PIs or NNRTIs, but not to INSTIs
Virologic Efficacy Against EVG- or RAL-Resistant HIV	*In vitro* data indicate activity, but clinical trial data are not available.	Yes, for some isolates; effective with DTG 50 mg twice-daily dose	No	No
Adverse Effects	Nausea, diarrhea (GI disturbance greater with EVG/c), headache, insomnia. Among ARV-naive individuals, initiation of INSTI-containing regimens has been associated with greater weight gain than NNRTI or boosted PI regimens (see text). Depression and suicidality are rare, occurring primarily in patients with pre-existing psychiatric conditions.			
	↑ CPK (4%)	Hypersensitivity, hepatotoxicity, ↑ CPK, myositis	↑ TG, ↑ LDL	↑ CPK, myopathy, hypersensitivity, SJS/TEN
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate	CYP3A4 substrate (minor)	EVG is a CYP3A4 substrate; COBI is a CYP3A4 inhibitor	No
Chelation with Polyvalent Cation Supplements and Antacids	Oral absorption of all INSTIs may be reduced by polyvalent cations. See Table 21d for recommendations regarding dosing separation of INSTIs and these drugs.			
Other Key Potential Drug Interactions	UGT1A1 substrate, OCT2 and MATE1 inhibitor	P-gp substrate, UGT1A1 substrate	EVG is a UGT1A1 substrate; COBI is a P-gp inhibitor.	UGT1A1 substrate

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BID = twice daily; COBI = cobicistat; CPK = creatine phosphokinase; CYP = cytochrome P; DRV = darunavir; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; GI = gastrointestinal; INSTI = integrase strand transfer inhibitor; LDL = low density lipoprotein; MATE = multidrug and toxic compound extrusion; NNRTI = non-nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; OAT = organic cation transporter; P-gp = p-glycoprotein; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RAL = raltegravir; SJS/TEN = Stevens Johnson Syndrome/toxic epidermal necrolysis; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglyceride; UGT = uridine diphosphate glucuronosyltransferase

Summary

Four INSTIs—BIC, DTG, EVG, and RAL—are approved for use in ART-naive patients with HIV.

The Panel recommends one of the following INSTI-based regimens for most people with HIV:

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)**—if HLA-B*5701 negative
- DTG plus (TAF or TDF) with (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF) with (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)
- DTG/3TC **(AI)**, except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

Among the INSTI-based regimens, RAL-containing regimens have the longest clinical experience, and they have been shown to have durable virologic efficacy; however, they have a higher pill burden than BIC- and DTG-containing regimens. EVG and RAL have lower barriers to resistance than BIC and DTG. Because of its high barrier to resistance, DTG plus two NRTIs or BIC/TAF/FTC may be considered for patients who must start ART before resistance test results are available. EVG-based regimens require boosting with COBI, which results in a greater potential for interaction with concomitant medications, Therefore, EVG-based regimens are now considered *Recommended Initial Regimens in Certain Clinical Situations*.

All INSTIs are generally well tolerated, though there are reports of insomnia in some patients. Depression and suicidal ideation, primarily in patients with a history of psychiatric illnesses, have rarely been reported in patients receiving INSTI-based regimens.[104-107]

Among ARV-naive individuals, initiation of INSTI-containing regimens has been associated with greater weight gain than NNRTI- or boosted PI-regimens.[23-26,108,109] In randomized trials of ARV-naive individuals, the mean increase in weight from baseline associated with BIC and DTG was similar and greater than with EVG/c.[23] Greater weight gain has also been observed after initiation of TAF,[20,23,24] or with a switch from TDF to TAF[74] especially in conjunction with INSTIs. While ARV-associated weight gain appears to disproportionately affect women, Blacks and Hispanics,[23,24,108,110] predictors and mechanism(s) for the weight gain are still unclear. Further questions that need to be clarified include regional distribution of the weight gain,[22] whether it is associated with significant cardio-metabolic risk,[111] and whether it is reversible upon discontinuation of the offending agent.

Preliminary data from an observational study in Botswana suggested that there may be an increased risk of NTDs in infants born to individuals who were receiving DTG at the time of conception.[5,9] Additional data show that the prevalence of NTDs in infants who were exposed to DTG at the time of conception is lower than previously reported, but still higher than in infants exposed to non-DTG regimens.[6,7] Before initiating an INSTI-based regimen in a person of childbearing potential, clinicians should review the information in Table 6b.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen for Most People with HIV

Bictegravir (BIC)

BIC is an INSTI that is approved by FDA for initial therapy in adults with HIV as a component of a single-tablet, once-daily regimen with TAF and FTC.

Efficacy in Clinical Trials:

- The efficacy of BIC in ART-naive adults has been evaluated in two large Phase 3 randomized double-blind clinical trials that compared BIC to DTG administered in combination with two NRTIs. The primary

efficacy endpoint was the proportion of participants with plasma HIV RNA <50 copies/mL at week 48.

- The GS-US-380-1490 trial randomized participants 1:1 to receive either BIC/TAF/FTC or DTG with coformulated TAF/FTC. Both regimens were given once daily. At week 96, 84% of participants in the BIC arm and 86% of those in the DTG arm achieved HIV RNA <50 copies/mL.[20]
- The GS-US-380-1489 trial randomized participants 1:1 to receive BIC/TAF/FTC or coformulated DTG/ABC/3TC once daily. At week 96, 88% of participants in the BIC/TAF/FTC arm and 90% of those in the DTG/ABC/3TC arm achieved HIV RNA <50 copies/mL.[21]

Adverse Effects:

- BIC is generally well tolerated. In clinical trials, the most commonly reported adverse reactions of any grade with an incidence ≥5% included diarrhea, nausea, and headache. Some studies have shown greater weight gain among people initiating INSTI-based regimens, particularly Black women. In a pooled analysis of eight randomized, controlled trials in ART-naive individuals, the weight gain at 96 weeks with BIC- and DTG-based regimens was similar (approximately 3.5 kg).[23]

Other Factors and Considerations:

- BIC is a CYP3A4 substrate and a UGT1A1 substrate, and its metabolism may be affected by concomitant use of CYP3A4 and UGT1A1 inducers or inhibitors. Rifampin or other rifamycins may decrease BIC or TAF concentrations, which may result in a loss of therapeutic effect. For patients who require rifamycins, BIC/FTC/TAF should not be used. Use of certain anticonvulsants and St. John's wort should also be avoided.[112]
- BIC is an inhibitor of the drug transporters OCT2 and MATE1, which may lead to increased concentrations of drugs that are substrates of these transporters. For this reason, dofetilide is **contraindicated** with BIC/TAF/FTC.
- BIC is not a CYP3A4 inducer or inhibitor; thus, unlike EVG/c, BIC is unlikely to affect the metabolism of medications that are CYP3A4 substrates.
- Like other INSTIs, oral absorption of BIC may be reduced when BIC is coadministered with polyvalent cations (e.g., aluminum-, magnesium-, or calcium-containing antacids, or calcium or iron supplements). See the BIC product label for dosing recommendations when using BIC with these products.[112]
- BIC decreases tubular secretion of creatinine without affecting glomerular function. Increases in serum creatinine are typically observed within the first 4 weeks of BIC therapy (with a median increase of 0.10 mg/dL after 48 weeks). This increase is comparable to that seen with other drugs that have a similar effect on creatinine secretion, including DTG, RPV, and COBI.
- Treatment-emergent mutations that confer BIC resistance have not yet been reported in people receiving BIC for initial therapy. BIC has not been studied in people with prior INSTI failure or INSTI-related resistance mutations, and BIC should not be used in these individuals until more data are available.
- There are insufficient data to determine whether use of BIC around the time of conception and during pregnancy is safe.

The Panel's Recommendation:

- On the basis of clinical trial data, the Panel categorizes the combination of BIC/TAF/FTC administered once daily as a *Recommended Initial Regimen for Most People with HIV* **(AI)**.
- Before prescribing BIC to a person of childbearing potential, review Table 6b. BIC should not be used in pregnancy because of insufficient safety data.

Dolutegravir (DTG)

DTG is an INSTI with a higher barrier to resistance than EVG or RAL. In ART-naive patients, DTG plus two NRTIs demonstrated high efficacy in achieving HIV suppression. DTG is given once daily, with or without food. Preliminary data from Botswana suggested that there may be an increased risk of NTDs in infants born to women who were receiving DTG at the time of conception,[5,9] but additional data indicate the risk is lower than previously reported.[6,7] More detailed discussions of this potential risk and recommendations for the use of DTG are found below and in Table 6b.

Efficacy in Clinical Trials:

- The efficacy of DTG in ART-naive patients has been evaluated in several fully powered randomized controlled clinical trials. In these trials, DTG-based regimens were noninferior or superior to a comparator INSTI-, NNRTI-, or PI-based regimen. The primary efficacy endpoint in these clinical trials was the proportion of participants with plasma HIV RNA <50 copies/mL.

DTG plus Two NRTIs versus Other INSTIs plus Two NRTIs:

- DTG-based regimens (with TAF/FTC or ABC/3TC) have been compared to BIC/TAF/FTC in two randomized controlled trials. These regimens have shown virologic efficacy that is similar to BIC/TAF/FTC (see the discussion in the BIC section above).[20,21,113,114]
- The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily. Each drug was administered in combination with an investigator-selected, two-NRTI combination (ABC/3TC or TDF/FTC) to 822 participants. At week 96, DTG was noninferior to RAL.[86]

DTG plus Two NRTIs versus EFV plus Two NRTIs:

- The SINGLE trial compared DTG 50 mg once daily plus ABC/3TC to EFV/TDF/FTC in 833 participants. At week 48, DTG plus ABC/3TC was superior to EFV/TDF/FTC, primarily because the study treatment discontinuation rate was higher in the EFV arm than in the DTG arm.[46] At week 144, DTG plus ABC/3TC remained superior to EFV/TDF/FTC.[115]
- The ADVANCE trial, an open label, noninferiority trial conducted in South Africa, compared DTG with either TDF/FTC or TAF/FTC to EFV/TDF/FTC. At week 48, the DTG-based regimens were noninferior to the EFV regimen based on the proportion of participants with HIV-RNA levels <50 copies/mL. More participants discontinued the trial regimen in the EFV group than in the DTG group.[24]
- The NAMSAL ANRS 12313 study, an open-label, multicenter randomized noninferiority trial conducted in Cameroon, compared DTG to EFV 400 mg, both combined with TDF/3TC. At week 48, DTG was noninferior to EFV 400 mg, with HIV RNA <50 copies/mL in 74.5% and 69.0% of participants in the DTG and EFV arms respectively.[8]

DTG plus Two NRTIs versus PI/r plus Two NRTIs:

- The FLAMINGO study, a randomized open-label clinical trial, compared DTG 50 mg once daily to DRV/r 800 mg/100 mg once daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 48, DTG was superior to DRV/r, with 90% and 83% of participants achieving HIV RNA <50 copies/mL, respectively. The rate of participants who discontinued their assigned regimen was higher in the DRV/r arm.[116] The difference in efficacy between the DTG and DRV/r regimens was more pronounced in patients with pretreatment HIV RNA levels >100,000 copies/mL. At week 96, DTG remained superior to DRV/r.[117]
- The ARIA trial, an open-label, Phase 3b randomized controlled trial, compared the efficacy and safety of DTG/ABC/3TC to ATV/r plus TDF/FTC in ART-naive, nonpregnant women. At week 48, 82% of participants in the DTG group and 71% in the ATV group ($P = 0.005$) achieved HIV RNA viral loads <50

copies/mL. The difference was driven by a lower rate of virologic nonresponse and fewer withdrawals due to adverse events in the DTG group.[118]

DTG/3TC:

- In the GEMINI-1 and GEMINI-2 trials, 1,433 ART-naive participants with baseline HIV RNA <500,000 copies/mL and no evidence of HBV infection were randomized to receive DTG plus 3TC or DTG plus TDF/FTC. At week 96, DTG plus 3TC was noninferior to DTG plus TDF/FTC based on the proportion of participants with viral loads <50 copies/mL (86% in DTG plus 3TC group and 89.5% in DTG plus TDF/FTC group).[4] Virologic nonresponse was uncommon, occurring in 3.1% of participants who received DTG plus 3TC and 2% of participants who received DTG plus TDF/FTC. No instances of treatment-emergent NRTI or INSTI resistance occurred in either treatment group. Among participants who started the study with CD4 counts <200 cells/mm^3, the rate of those with HIV RNA <50 copies/mL at week 96 was lower in the DTG plus 3TC group than in the DTG plus TDF/FTC group; however, the difference was not related to a higher rate of virologic failures in the two-drug group.

- Two other small, non-randomized single-arm studies showed similar rates of viral suppression with DTG plus 3TC.[119,120]

Adverse Effects:

- DTG is generally well tolerated. The most commonly reported adverse reactions of moderate-to-severe intensity were insomnia and headache. As discussed earlier, some studies have shown greater weight gain among people initiating INSTI-based regimens, including regimens with DTG.[23-26]

- Case series of neuropsychiatric adverse events (e.g., sleep disturbances, depression, anxiety, suicidal ideation) associated with the initiation of DTG and RAL have been reported.[104,105] Two observational cohort studies reported a higher frequency of neuropsychiatric adverse events leading to treatment discontinuation in patients receiving DTG than in patients receiving other INSTIs.[106,107] However, analyses of data from large randomized controlled trials and a health care database demonstrated similar rates of neuropsychiatric adverse events between DTG-based regimens and other ARV regimens,[121] with neuropsychiatric events rarely leading to DTG discontinuation. Another report from the World Health Organization international pharmacovigilance database reported neuropsychiatric events with all approved INSTIs,[122] not just DTG. Further studies will be needed to clarify the true incidence and implications of these neuropsychiatric events. A pathophysiologic mechanism for these neuropsychiatric adverse events has not been defined.

- An observational surveillance study of birth outcomes among pregnant women on ART in Botswana identified five cases of NTDs among infants born to 1,683 women (0.3%) who initiated a DTG-based regimen around the time of conception. The incidence of NTDs among infants born to women who were receiving other ARV drugs at the time of conception was 0.1%, although data were limited for all other ARV agents except EFV.[9] See Table 6b for recommendations on prescribing INSTIs as part of initial therapy, including for people of childbearing potential.

- Weight gain has been reported with INSTIs, including DTG, as discussed in the Summary of this INSTI section.

Other Factors and Considerations:

- DTG, like BIC, decreases tubular secretion of creatinine without affecting glomerular function, with increases in serum creatinine observed within the first 4 weeks of treatment.

- DTG has fewer drug interactions than EVG/c. See Drug-Drug Interactions for specific drug-drug interactions that require dosage adjustment.

- DTG absorption, like absorption for other INSTIs, may be reduced when the ARV is coadministered with polyvalent cations (see Drug-Drug Interactions). DTG should be taken at least 2 hours before or 6 hours after cation-containing antacids or laxatives are taken. Alternatively, DTG and supplements containing calcium or iron can be taken simultaneously with food.
- Treatment-emergent mutations that confer DTG resistance have been rarely reported in patients receiving DTG as part of a three-drug regimen for initial therapy.[17-19] The incidence of resistance with DTG is much lower than with EVG or RAL, which suggests that DTG, like BIC, has a higher barrier to resistance than EVG or RAL.

The Panel's Recommendations:

- On the basis of clinical trial data, the Panel categorizes DTG in combination with ABC/3TC **(AI)**, TAF/FTC **(AI)**, or TDF/(FTC or 3TC) **(AI)** as a *Recommended Initial Regimen for Most People with HIV*.
- The Panel also recommends the use of DTG/3TC **(AI)** as a *Recommended Initial Regimen for Most People with HIV* except for those with HIV RNA >500,000 copies/mL, with HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or of HBV testing are available.
- Individuals of childbearing potential should have a pregnancy test before initiating DTG **(AIII)**.
- A DTG-based regimen can be considered for individuals of childbearing potential who are using effective contraception after a discussion of the risks and benefits of the regimen so that individuals can make informed decisions (see Table 6b for details) **(BIII)**.
- For initial therapy of individuals of childbearing potential who are trying to conceive or are sexually active and not using contraception, please see Table 6b for recommendations.

Raltegravir (RAL)

RAL was the first INSTI approved for use in both ARV-naive and ARV-experienced patients.

Efficacy in Clinical Trials

RAL 400 mg Twice Daily plus Two NRTIs versus Comparator Drug plus Two NRTIs:

- The efficacy of RAL at a dose of 400 mg twice daily (with either TDF/FTC or ABC/3TC) as initial therapy was evaluated in two randomized, double-blind, controlled clinical trials and a third open-label, randomized trial.
    - STARTMRK compared RAL 400 mg twice daily to EFV 600 mg once daily, each administered in combination with TDF/FTC. RAL was noninferior to EFV at 48 weeks.[82] RAL was superior to EFV at 4 and 5 years,[85,123] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
    - The SPRING-2 trial compared DTG 50 mg once daily to RAL 400 mg twice daily, each administered in combination with investigator-selected ABC/3TC or TDF/FTC. At week 96, DTG was noninferior to RAL.
    - The SPRING-2 trial also provided nonrandomized data on the efficacy of RAL plus ABC/3TC. In this trial, 164 participants (39 participants with baseline viral loads ≥100,000 copies/mL and 125 participants with baseline viral loads <100,000 copies/mL) received RAL in combination with ABC/3TC. After 96 weeks, there was no difference in virologic response between the ABC/3TC and TDF/FTC groups when RAL was given as the third drug.[86]
    - ACTG A5257, a large randomized open-label trial, compared three NNRTI-sparing regimens

that contained RAL, ATV/r, or DRV/r, each given with TDF/FTC. At week 96, all three regimens had similar virologic efficacy, but RAL was superior to both ATV/r and DRV/r for the combined endpoints of virologic efficacy and tolerability. Participants had greater increases in lipid levels in the ritonavir-boosted protease inhibitor (PI/r) arms than in the RAL arm, and BMD decreased to a greater extent in participants in the PI/r arms than in participants in the RAL arm.[13]

RAL 1,200 mg Once Daily plus TDF/FTC versus RAL 400 mg Twice Daily plus TDF/FTC:

- In a Phase 3, randomized, double-blind, active comparator-controlled trial (the ONCEMRK trial), the efficacy of once-daily RAL 1,200 mg (formulated as two 600-mg tablets) was compared to RAL 400 mg twice daily, each administered with TDF/FTC. At 96 weeks, a similar proportion of participants in both groups achieved HIV RNA suppression (81.5% in the once-daily arm vs. 80.1% in the twice-daily arm). The responses were similar regardless of baseline HIV RNA or CD4 count.[124]

Adverse Effects:

- RAL, when compared in a randomized trial to DRV/r or ATV/r, all with TDF/FTC, led to a greater mean increase in waist circumference.[125]
- RAL use has been associated with creatine kinase elevations. Myositis and rhabdomyolysis have been reported.
- Rare cases of severe skin reactions and systemic HSRs in patients who received RAL have been reported during post-marketing surveillance.[126]
- Neuropsychiatric adverse events (e.g., insomnia, headache, depression, and suicidal ideation) have been reported in people receiving INSTIs (see the discussion under DTG).[121,127]

Other Factors and Considerations:

- RAL can be administered as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily with or without food in ART-naive patients.
- Coadministration of RAL as either 400 mg twice daily or 1,200 mg once daily with aluminum-containing and/or magnesium-containing antacids **is not recommended**. Calcium carbonate-containing antacids may be coadministered with RAL 400 mg twice daily, but not with RAL 1,200 mg once daily. Polyvalent cation-containing supplements may also reduce absorption of RAL. See Table 21d for dosing recommendations.
- RAL has a lower barrier to resistance than RTV-boosted PIs, BIC, and DTG.
- Among those who received RAL during pregnancy, the rate of fetal malformations is within the expected range for pregnancy outcomes in the United States.[10-12] Data on RAL use around the time of conception is limited. Thus far, based on data collected from Antiretroviral Pregnancy Registry, the manufacturer and in a cohort study from the United States and other countries, no case of NTD has been reported.[10-12]

The Panel's Recommendations:

- On the basis of these clinical trial data, the Panel considers RAL given as 1,200 mg (two 600-mg tablets) once daily or as 400 mg twice daily plus TDF/FTC **(BI)** or TAF/FTC **(BII)** as a *Recommended Initial Regimen for Most People with HIV*.

Integrase Strand Transfer Inhibitors Recommended as Part of an Initial Regimen in Certain Clinical Situations

Elvitegravir (EVG)

EVG is available as a component of two STRs: EVG/c/TDF/FTC and EVG/c/TAF/FTC. COBI is a specific,

potent CYP3A inhibitor that has no activity against HIV. It acts as a PK enhancer of EVG, which allows for once-daily dosing of the combination but increases the likelihood of significant drug interactions.

Efficacy in Clinical Trials:

- The efficacy of EVG/c/TDF/FTC in ART-naive participants has been evaluated in two randomized, double-blind active-controlled trials.
  - At 144 weeks, EVG/c/TDF/FTC was noninferior to fixed-dose EFV/TDF/FTC.[128]
  - EVG/c/TDF/FTC was also found to be noninferior to ATV/r plus TDF/FTC.[129]
  - In a randomized, blinded trial that compared EVG/c/TDF/FTC to ATV/r plus TDF/FTC in women with HIV, EVG/c/TDF/FTC had superior efficacy, in part because of a lower rate of treatment discontinuation.[15]
- The efficacy of EVG/c/TAF/FTC in ART-naive participants has been evaluated in two randomized, double-blind controlled trials in adults with eGFR ≥50 mL/min.[47,50]
  - At 48 and 96 weeks, TAF was noninferior to TDF when both drugs were combined with EVG/c/FTC; at 144 weeks, EVG/c/TAF/FTC was superior to EVG/c/TDF/FTC.[48]

Adverse Effects:

- The most common adverse events reported with EVG/c/TDF/FTC were diarrhea, nausea, upper respiratory infection, and headache.[128,129]
- The most common adverse events reported with EVG/c/TAF/FTC were nausea, diarrhea, headache, and fatigue.[130]
- Neuropsychiatric adverse events have been reported in people receiving INSTIs (see the discussion under DTG).

Other Factors and Considerations:

- EVG is metabolized primarily by CYP3A enzymes; as a result, CYP3A inducers or inhibitors may alter EVG concentrations.
- Because COBI is a PK enhancer, it is a CYP3A enzyme inhibitor, which may lead to significant interactions with medications that are metabolized by this enzyme (see Drug-Drug Interactions).[131]
- Administration of EVG simultaneously with polyvalent cation-containing antacids or supplements lowers EVG plasma concentrations (see Drug-Drug Interactions). Separate EVG/c/TDF/FTC or EVG/c/TAF/FTC and polyvalent antacid administration by at least 2 hours; administer polyvalent cation-containing supplements at least 2 hours before or 6 hours after EVG.
- COBI inhibits active tubular secretion of creatinine, resulting in increases in serum creatinine and a reduction in estimated CrCl without reducing glomerular function.[132] Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline while taking EVG/c/TDF/FTC should be closely monitored and evaluated for evidence of TDF-related proximal renal tubulopathy.[99]
- EVG/c/TDF/FTC **is not recommended** for patients with pretreatment estimated CrCl <70 mL/min.[99]
- EVG/c/TAF/FTC **is not recommended** for patients with estimated CrCl <30 mL/min unless they are on chronic hemodialysis. An observational study of 55 people with HIV who were on hemodialysis suggested that EVG/c/TAF/FTC given once daily (after hemodialysis on dialysis days) can be used safely in persons with no resistance to any of the ARV drugs in this STR.[133]
- At the time of virologic failure, INSTI-associated mutations were detected in some EVG/c/TDF/FTC-

treated patients whose therapy failed.[128,129] These mutations conferred cross-resistance to RAL, with most patients retaining susceptibility to DTG.

- EVG/c **is not recommended** during pregnancy because of low drug exposure when taken during the second and third trimesters.[134]

The Panel's Recommendation:

- On the basis of the above considerations, the Panel classifies EVG/c/TAF/FTC and EVG/c/TDF/FTC as *Recommended Initial Regimens in Certain Clinical Situations* **(BI)**. EVG/c/TAF/FTC should only be used in people with estimated CrCl ≥30 mL/min, unless they are on chronic hemodialysis. EVG/c/TDF/FTC should only be used in people with estimated CrCl ≥70 mL/min.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Table 8c. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors that are Recommended for Antiretroviral Therapy-Naive Patients

Characteristics	DOR	EFV	RPV
Dosing Frequency	Once daily	Once daily	Once daily
Food Requirement	With or without food	On an empty stomach	With a meal
STR Available for ART-Naive Patients	DOR/TDF/3TC	• EFV 600 mg/TDF/FTC • EFV 600 mg/TDF/3TC • EFV 400 mg/TDF/3TC	• RPV/TAF/FTC • RPV/TDF/FTC
Available as a Single-Drug Tablet	Yes	Yes	Yes
Adverse Effects	Generally well tolerated	• CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, insomnia, somnolence • Skin rash • QTc prolongation	• Depression, headache • Skin rash • QTc prolongation
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate	CYP3A4 substrate, mixed inducer/inhibitor	CYP3A4 substrate
Other Significant Drug Interactions	None	CYP2B6 and 2C19 inducer	RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is not recommended; see Drug-Drug Interactions for dosing recommendations when RPV is coadministered with H2 blocker or antacids.

Key: 3TC = lamivudine; CNS = central nervous system; CYP = cytochrome P; DOR = doravirine; EFV = efavirenz; FTC = emtricitabine; H2 = histamine 2; PPI = proton pump inhibitor; RPV = rilpivirine; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Summary

Five NNRTIs (delavirdine [DLV], DOR, EFV, etravirine [ETR], NVP, and RPV) are currently approved by FDA for the treatment of HIV when used in combination with other ARV drugs.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs (especially EFV and RPV) are the prevalence of NNRTI-resistant viral strains in ART-naive patients[135] and the drugs' low barrier for the development of resistance. Resistance testing should be performed before initiation of an NNRTI-based regimen in ART-naive patients. High-level resistance to

all NNRTIs (except ETR or DOR) may occur with a single mutation. In RPV-treated patients, the presence of RPV resistance mutations at virologic failure may confer cross-resistance to other NNRTIs, including ETR.[136,137] DOR-, EFV-, and RPV-based regimens are now categorized as *Recommended Initial Regimens in Certain Clinical Situations* for ART-naive patients.

Doravirine (DOR)

Efficacy in Clinical Trials

The efficacy of DOR-based therapy for treatment of HIV in ART-naive individuals was demonstrated in two randomized, double-blind, placebo-controlled trials.

DOR-Based Regimen versus EFV-Based Regimen:

- In DRIVE-AHEAD, 734 participants received either DOR/TDF/3TC or EFV/TDF/FTC, both as FDCs.[36]
    - At 48 weeks, DOR/TDF/3TC was noninferior to EFV/TDF/FTC, with 84.3% of participants who received DOR/TDF/3TC and 80.8% of those who received EFV/TDF/FTC achieving HIV RNA <50 copies/mL. Although virologic responses to ART overall were lower in participants with pre-ART HIV RNA >100,000 copies/mL, there was no difference between the DOR-treated and EFV-treated participants. Virologic responses overall were lower in participants with pre-ART HIV RNA >100,000 copies/mL, but there was no difference between the DOR and EFV groups.
    - A greater proportion of participants in the EFV arm discontinued their assigned ART due to adverse events than in the DOR arm (6.3% vs. 2.7%). Neuropsychiatric side effects were more common in the EFV arm.
    - Genotype resistance results were reported for 13 participants with virologic failure in the DOR arm and 10 participants in the EFV arm. For the DOR arm, seven out of 13 participants had NNRTI resistance and five out of 13 had NRTI resistance; for EFV, nine out of 10 participants had NNRTI resistance and five out of 10 had NRTI resistance.
    - LDL cholesterol and non-HDL cholesterol did not change with DOR use, whereas both increased with EFV use.
    - At 96 weeks, 77.5% and 73.6% of participants in the DOR arm and the EFV arm had maintained HIV RNA <50 copies/mL, respectively.[138]

DOR-Based Regimen versus DRV/r-Based Regimen:

- In DRIVE-FORWARD, 769 participants received DOR or DRV/r once daily along with two investigator-selected NRTIs, either ABC/3TC or TDF/FTC.[37]
    - At 48 weeks, DOR was found to be noninferior to DRV/r when these drugs were administered with two NRTIs, with 84% of study participants receiving DOR versus 80% of those receiving DRV/r achieving HIV RNA <50 copies/mL at 48 weeks.
    - Participants who received DOR plus ABC/3TC (n = 48) and those who received DOR plus TDF/FTC (n = 316) had similar virologic responses.
    - At week 96, DOR was superior to DRV/r in terms of virologic suppression,[139] with a higher rate of discontinuation in the DRV/r group.
    - Genotype resistance results were reported for seven and eight participants with virologic failure in the DOR and DRV/r arms, respectively. No drug resistance mutations were detected in either group.
    - Treatment-related diarrhea was more frequently reported in the DRV/r arm, and greater increases in fasting LDL cholesterol and triglycerides were seen in the participants who received DRV/r than in those who received DOR.

Other Factors and Considerations:

- DOR is available as a single-drug, 100-mg tablet[140] and as part of an STR that contains DOR/TDF/3TC 100 mg/300 mg/300 mg[141] and is dosed once daily, with or without food.
- DOR is primarily metabolized by the CYP3A4 enzyme and should not be coadministered with strong CYP3A4 inducers. DOR concentration may increase in the presence of a CYP3A4 inhibitor (see Table 21b). DOR is not a CYP3A4 inducer or inhibitor, so it is not expected to affect the concentrations of concomitant CYP3A4 substrates.
- Treatment-emergent resistance mutations to DOR may confer cross-resistance to certain other NNRTIs. Most isolates with DOR mutations remain susceptible to ETR.[142]
- DOR-based regimens have not been directly compared to INSTI-based regimens in clinical trials.
- There are currently no data on the safety of DOR use during pregnancy.

The Panel's Recommendations:

- On the basis of the clinical trial data discussed above, the Panel classifies DOR/TDF/3TC **(BI)** and DOR plus two NRTIs (**BI** for TDF/FTC and **BIII** for TAF/FTC) as *Recommended Initial Regimens in Certain Clinical Situations*.
- Because the number of clinical trial participants who received DOR plus ABC/3TC is much lower than the number who received TDF/FTC plus DOR, the Panel considers ABC/3TC plus DOR to be an option for initial therapy **(CI)**.

Efavirenz (EFV)

Efficacy of EFV 600 mg Daily Dose in Clinical Trials:

- Large randomized controlled trials and cohort studies in ART-naive patients have demonstrated potent and durable viral suppression in patients treated with EFV plus two NRTIs. EFV-based regimens have demonstrated superiority or noninferiority to a number of comparator regimens in ART-naive patients in several randomized controlled trials.
- In ACTG 5202, EFV was comparable to ATV/r when each was given with either TDF/FTC or ABC/3TC.[143]
- In the ECHO and THRIVE studies, EFV was noninferior to RPV, with less virologic failure. However, EFV caused more discontinuations due to adverse events. The virologic advantage of EFV was most notable in participants with pre-ART viral loads >100,000 copies/mL, and NRTI and NNRTI resistance occurred more frequently in patients who experienced failure on a regimen that included RPV.[144]
- In the GS 102 study, EFV/TDF/FTC was noninferior to EVG/c/TDF/FTC.[128]
- The DRIVE-AHEAD study compared EFV/TDF/FTC to DOR/TDF/3TC in ART-naive patients. At 48 weeks, DOR/TDF/3TC was found to be noninferior to EFV/TDF/FTC, as discussed in the DOR section. Neuropsychiatric side effects were more common in the EFV arm.
- ADVANCE, an open label, noninferiority trial, compared TDF/FTC/EFV 600 mg to DTG combined with either TDF/FTC or TAF/FTC. At week 48, the DTG regimens were noninferior to the EFV regimen based on the proportion of participants with HIV-RNA levels <50 copies/mL. More participants in the EFV group than in the DTG group discontinued the trial regimen.[24]

In clinical trials, some regimens have demonstrated superiority to those with EFV, based primarily on fewer discontinuations because of adverse events:

- In the SINGLE trial, a DTG-based regimen was superior to an EFV regimen at the primary endpoint of viral suppression at week 48.[46]
- In the STARTMRK trial, RAL was noninferior to EFV at 48 weeks,[82] but RAL was superior to EFV at 4 and 5 years,[85,123] in part because of more frequent discontinuations due to adverse events in the EFV group than in the RAL group.
- In the open-label STaR trial, participants with baseline viral loads ≤100,000 copies/mL had higher rates of treatment success on RPV than on EFV.[145]

Efficacy of Low-Dose Efavirenz (EFV 400 mg Daily) in Clinical Trials:

- ENCORE 1, a multinational, randomized, placebo-controlled trial, compared two once-daily doses of EFV (combined with TDF/FTC): EFV 600 mg (standard dose) versus EFV 400 mg (reduced dose). At 96 weeks, EFV 400 mg was noninferior to EFV 600 mg for rate of viral suppression.[35] While the frequency of overall adverse events was not different between groups, EFV-related adverse events and treatment-related discontinuations occurred less frequently in the EFV 400 mg group than in the EFV 600 mg group. Although there were fewer self-reported CNS events in the 400 mg group, the groups had similar rates of psychiatric events. The 400-mg dose of EFV is now approved in the United States for initial treatment of HIV infection and is coformulated with TDF and 3TC in an FDC tablet.
- NAMSAL ANRS 12313 (an open-label, multicenter randomized noninferiority trial) compared EFV 400 mg to DTG, both combined with TDF/3TC. At week 48, EFV 400 mg was noninferior to DTG based on percentage of participants with viral suppression to HIV RNA <50 copies/mL (69.0% in EFV group vs. 74.5% in DTG group).[8]
- In an open label trial, 25 pregnant women with HIV and HIV RNA <50 copies/mL while on an EFV-based regimen were switched from EFV 600 mg to EFV 400 mg daily (the TDF and FTC or 3TC components of the regimen did not change). Participants were monitored closely with EFV concentrations measured weekly and viral loads biweekly during pregnancy and postpartum. Stopping criteria were HIV RNA >50 copies/mL on two consecutive occasions or random EFV concentration <800 ng/mL on three consecutive occasions. All participants maintained viral load suppression to HIV RNA <50 copies/mL throughout the study.[146]
- A PK study enrolled 22 persons with HIV (without TB) who were on an EFV-based regimen and had HIV RNA levels <50 copies/mL. Participants were switched from EFV 600 mg to EFV 400 mg. Fourteen days after the switch, isoniazid and rifampin were started for 12 weeks. The combination resulted in only minimal reduction in EFV 400 mg PK parameters, which were within the range of concentrations seen in the ENCORE 1 trial. HIV RNA levels <50 copies/ mL were maintained in all participants during the study.[147]

Adverse Effects:

- EFV can cause CNS side effects (e.g., abnormal dreams, dizziness, headache, and depression) that resolve over a period of days to weeks in most patients. However, subtler, long-term neuropsychiatric effects can occur.
- EFV use has also been associated with suicidality; however, evidence for this association has differed among various large studies. An analysis of four ACTG comparative trials showed a higher rate of suicidality (i.e., reported suicidal ideation or attempted or completed suicide) among EFV-treated patients than among patients taking comparator regimens (LPV/r, ATV, ATV/r, or ABC-based regimens).[148] Similarly, a subgroup analysis of the START trial revealed higher risk of suicidal or self-injurious behavior among participants in the immediate ART group who took EFV than among ART-naive controls; the risk increased for those with previous psychiatric diagnoses.[149] This association, however,

was not found in analyses of three large observational cohorts[150,151] or in a retrospective cohort study that used U.S. administrative pharmacy claims data.[152] A prospective observational cohort study among people with HIV in Uganda revealed no evidence that EFV carried a greater risk of suicidal ideation or depression than NVP.[153]

- Delayed onset neurotoxicities, including ataxia and encephalopathy, have been reported months to years after EFV use.[154,155]
- EFV may cause elevation in LDL cholesterol and triglycerides.
- QTc interval prolongation has been observed with EFV use.[156,157] Consider an alternative to EFV in patients taking medications known to increase the risk of Torsades de Pointes, or in patients at higher risk of Torsades de Pointes.

Other Factors and Considerations:

- EFV is formulated both as a single-drug, 600-mg tablet and in an FDC tablet of EFV/TDF/FTC that allows for once-daily dosing.
- EFV is also available as a generic single-drug, 600-mg tablet and as a generic once-daily FDC tablet that includes 3TC, TDF, and either 600 mg or 400 mg of EFV; the lower-dose EFV/TDF/3TC tablet is approved for treating adults and children weighing ≥35 kg.[158,159]
- EFV is a substrate of CYP3A4 and an inducer of CYP3A4 and 2D6, and therefore, may potentially interact with other drugs that use the same pathways (see Tables 21b, 22a, and 22b).
- EFV has been associated with CNS birth defects in nonhuman primates, and cases of NTDs have been reported after first-trimester exposure in humans.[160] A link between EFV and birth defects in humans has not been supported in meta-analyses (see the Perinatal Guidelines).[161]
- People with HIV who are taking a regimen that includes EFV should be screened for depression and suicidality.

The Panel's Recommendations:

- Given the availability of regimens with fewer treatment-limiting adverse events and noninferior or superior efficacy, the Panel classifies EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC **(BI)** or EFV 600 mg plus TAF/FTC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- Randomized clinical trial data have demonstrated the noninferiority of EFV 400 mg compared to EFV 600 mg[35] and to DTG.[8] This dose has not been studied in a U.S. population. The Panel classifies EFV 400 mg/TDF/3TC as a *Recommended Initial Regimen in Certain Clinical Situations* **(BI)**.

Rilpivirine (RPV)

RPV is an NNRTI that is approved for use in combination with NRTIs for ART-naive patients with pretreatment viral loads <100,000 copies/mL.

Efficacy in Clinical Trials:

- Two Phase 3 randomized, double-blind clinical trials—ECHO and THRIVE—compared RPV and EFV, each combined with two NRTIs.[144] At 96 weeks, the following findings were reported:
  - RPV was noninferior to EFV overall.
  - Among participants with pre-ART viral loads >100,000 copies/mL, more RPV-treated participants than EFV-treated participants experienced virologic failure. Moreover, in this subgroup of participants with virologic failure, NNRTI and NRTI resistance were more frequently identified in those treated with RPV.

- Among the RPV-treated participants, the rate of virologic failure was greater in those with pretreatment CD4 counts <200 cells/mm^3 than in those with CD4 counts ≥200 cells/mm^3.
- STaR, a Phase 3b, open-label study, compared the FDCs of RPV/TDF/FTC and of EFV/TDF/FTC in 786 treatment-naive patients. The results at 96 weeks[162] were similar to those reported at 48 weeks.[145]
  - RPV was noninferior to EFV overall.
  - RPV was superior to EFV in patients with pre-ART viral loads ≤100,000 copies/mL and noninferior in those with pre-ART viral loads >100,000 copies/mL. Among patients with pre-ART viral loads >500,000 copies/mL, virologic failure was more common in RPV-treated patients than in EFV-treated patients.
  - There were more participants with emergent resistance in the RPV/FTC/TDF arm than in the EFV/FTC/TDF arm (4% vs. 1%, respectively).
- The STR of RPV/TAF/FTC was approved by FDA based on results from a bioequivalence study. In this study, plasma concentrations of RPV, FTC, and TAF 25 mg in participants taking the coformulated drug were similar to those seen in participants who received RPV as the single-drug tablet and TAF/FTC as part of the STR of EVG/c/TAF 10 mg/FTC.[76]

Adverse Effects:

- RPV is generally well tolerated. In the ECHO, THRIVE, and STaR trials, fewer instances of CNS adverse events (e.g., abnormal dreams, dizziness, psychiatric side effects), skin rash, and dyslipidemia were reported in the RPV arms than in the EFV arms, and fewer patients in the RPV arms discontinued therapy due to adverse events. However, up to 9% of clinical trial participants experienced depressive disorders, including approximately 1% of participants who had suicidal thoughts or who attempted suicide. Patients receiving RPV who have severe depressive symptoms should be evaluated to assess whether the symptoms may be due to RPV and if the risks of continuing the same regimen outweigh the benefits.

Other Factors and Considerations:

- RPV is formulated both as a single-drug tablet and in STRs with TAF/FTC and with TDF/FTC. Among available STRs, RPV/TAF/FTC is the smallest tablet.
- RPV/TAF/FTC and RPV/TDF/FTC are given once daily and must be administered with a meal (containing at least 390 kcal).
- RPV is also coformulated as a once-daily FDC tablet with DTG that is used as continuation therapy for persons with HIV who have achieved viral suppression.[163] However, this combination has not been studied in ART-naive individuals, and it **is not recommended** for initial therapy (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression).
- The oral drug absorption of RPV can be significantly reduced in the presence of acid-lowering agents. RPV is **contraindicated** in patients who are receiving proton pump inhibitors (PPIs), and should be used with caution in those receiving H2 antagonists or antacids (see Drug-Drug Interactions for dosing recommendations).
- RPV is primarily metabolized in the liver by the CYP3A enzyme; its plasma concentration may be affected in the presence of CYP3A inhibitors or inducers (see Drug-Drug Interactions).
- At doses above the approved dose of 25 mg, RPV may cause QTc interval prolongation. RPV should be used with caution when coadministered with a drug known to increase the risk of Torsades de Pointes.

The Panel's Recommendations:

- Given the availability of other effective regimens that do not have virologic and immunologic prerequisites to initiate treatment, the Panel recommends RPV/TDF/FTC and RPV/TAF/FTC as *Recommended Initial Regimens in Certain Clinical Situations*.
- Use of RPV with TAF/FTC **(BII)** or TDF/FTC **(BI)** should be limited to ART-naive patients with pretreatment viral loads <100,000 copies/mL and CD4 counts >200 cells/mm^3.
- Data on RPV plus ABC/3TC are insufficient to consider recommending this regimen.

Protease Inhibitor-Based Regimens

Table 8d. Characteristics of Protease Inhibitor Options that are Recommended for Antiretroviral Therapy-Naive Patients

Characteristics	ATV	DRV
Dosing Frequency	Once daily	• Once daily for PI-naive patients • Twice daily for PI-experienced patients with certain PI mutations
PK Boosting	PK-boosting with RTV or COBI is generally recommended. Unboosted ATV is also FDA-approved for ART-naive patients.	DRV should only be used with a PK booster (i.e., RTV or COBI).
Fixed-Dose Formulation	• ATV/c	• DRV/c • DRV/c/TAF/FTC
Available as a Single-Drug Tablet	Yes	Yes
Adverse Effects	• Jaundice • Indirect hyperbilirubinemia • Cholelithiasis • Nephrolithiasis • PR prolongation	• Skin rash • Increase in serum transaminases • Hyperlipidemia • A higher cardiovascular risk was reported in participants taking DRV-based regimens than in those taking ATV-based regimens in an observational cohort study.
CYP3A4 Drug-Drug Interactions	CYP3A4 substrate, inhibitor	CYP34A substrate, inhibitor
Other Significant Drug Interactions	ATV absorption is reduced when ATV is given with acid-lowering therapies. See Table 21a for ATV dosing recommendations when the drug is coadministered with acid-lowering agents.	N/A

Key: ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; COBI = cobicistat; CYP = cytochrome P; DRV = darunavir; DRV/c = darunavir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; N/A = not applicable; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

Summary

FDA-approved PIs include ATV, atazanavir/cobicistat (ATV/c), DRV, DRV/c, FPV, IDV, LPV/r, nelfinavir, RTV, saquinavir (SQV), and tipranavir. PI-based regimens with PK enhancement (also called boosting) have demonstrated virologic potency, durability in treatment-naive patients, and a high barrier to resistance. Because transmitted PI resistance is uncommon, PI-based regimens are generally recommended if early ART initiation is necessary, before resistance test results are available. Few or no PI mutations are detected when a patient's first PI-based regimen fails, which is not the case with NNRTI-based regimens and some INSTI-based regimens.[164,165] For this reason, PI-based regimens may be useful for patients at risk for intermittent therapy because of poor adherence. All PIs (boosted by either RTV or COBI) inhibit the CYP3A4 isoenzyme,

which may lead to significant drug-drug interactions (see Drug-Drug Interactions). Each PI has specific characteristics related to its virologic potency, adverse effects profile, and PK properties. The characteristics of recommended PIs are listed in Table 9 and Appendix B, Table 5.

PI-based regimens that are recommended for use in ART-naive patients should have proven virologic efficacy, once-daily dosing, a lower pill count than older PI-based regimens, and good tolerability. On the basis of these criteria, the Panel considers once-daily DRV/r, DRV/c, ATV/c, or ATV/r, each administered in combination with with two NRTIs, as PI-based regimen options in the category of *Recommended Initial Regimens in Certain Clinical Situations*. DRV/c/TAF/FTC is now available as an STR. In a large, randomized controlled trial comparing DRV/r, ATV/r, and RAL, each administered in combination with TDF/FTC, all three regimens achieved similar virologic suppression rates; however, the proportion of patients who discontinued their assigned treatment because of adverse effects, mainly hyperbilirubinemia, was greater in the ATV/r arm than in the other two arms.[13]

Several metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which also depends on the dose of RTV used as a PK-enhancing agent. Large observational cohort studies found an association between some PIs (i.e., DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[29-31,34] Another observational cohort study of predominantly male participants found a lower rate of cardiovascular events in those receiving ATV-containing regimens than in those receiving other regimens.[33] Further study is needed.

Compared to other PIs, LPV/r, FPV/r, unboosted ATV, and SQV/r have disadvantages such as greater pill burden, lower efficacy, or increased toxicity, and thus are no longer recommended as options for initial therapy.

Darunavir/Ritonavir (DRV/r)

Efficacy in Clinical Trials:

- The ARTEMIS study compared DRV/r (800 mg/100 mg once daily) with LPV/r (800 mg/200 mg once daily or 400 mg/100 mg twice daily), both administered in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. DRV/r was noninferior to LPV/r at week 48,[80] and superior at week 192.[166] Among participants with baseline HIV RNA levels >100,000 copies/mL, virologic response rates were lower in the LPV/r arm than in the DRV/r arm.
- The FLAMINGO study compared DRV/r with DTG, each administered in combination with two NRTIs, in 488 ART-naive participants. The rate of virologic suppression at week 96 was significantly greater among those who received DTG than in those who received DRV/r. The higher rate of virologic failure observed in the DRV/r group was primarily related to the great number of failures among those with a viral load >100,000 copies/mL, and secondarily because there were more drug discontinuations in the DRV/r group.[14]
- ACTG A5257, a large, randomized, open-label trial, compared ATV/r to DRV/r or RAL, each given with TDF/FTC. The trial showed similar virologic efficacy for DRV/r, ATV/r, and RAL, but more participants in the ATV/r group discontinued randomized treatment because of adverse events.[13]
- The DRIVE-FORWARD study compared DRV/r to DOR, both administered with two investigator-selected NRTIs, in ART-naive participants. At 48 weeks, DOR was found to be noninferior to DRV/r, with 80% of participants who received DOR and 84% of participants who received DRV/r achieving HIV RNA levels <50 copies/mL.

Adverse Effects:

- Patients taking DRV/r may develop a skin rash, which is usually mild-to-moderate in severity and self-

limited. Treatment discontinuation is necessary on rare occasions when severe rash with fever or elevated transaminases occur.

- ACTG A5257 showed similar lipid changes in participants in the ATV/r and DRV/r arms. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[13] The likelihood of developing metabolic syndrome was equivalent between the three arms, although a larger increase in waist circumference was observed at 96 weeks in participants assigned to the RAL arm than in those assigned to the DRV/r arm ($P \leq 0.02$).[167]
- An observational cohort study suggested that DRV/r is associated with increased rates of cardiovascular disease.[34]

Other Factors and Considerations:

- DRV/r is administered once daily with food in treatment-naive patients.
- DRV has a sulfonamide moiety and should be used with caution in patients with severe sulfonamide allergies. In clinical trials, the incidence and severity of rash were similar in participants with and without a history of sulfonamide allergy. Most patients with sulfonamide allergy are able to tolerate DRV.
- DRV/r is a potent CYP3A4 inhibitor, and this may lead to significant interactions with other medications metabolized through this same pathway (see Drug-Drug Interactions).

The Panel's Recommendations:

- On the basis of efficacy and safety data from clinical trials and clinical experience, the Panel classifies DRV/r with TDF/FTC **(AI)**, with TAF/FTC **(AII)**, or with ABC/3TC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situations*.

Darunavir/Cobicistat (DRV/c)

In a study in healthy volunteers, DRV 800 mg with COBI 150 mg was bioequivalent to DRV 800 mg with RTV 100 mg based on the maximum concentration and area under the concentration time curve for DRV.[168] Because the minimum concentration (C_{min}) of DRV combined with COBI was 31% lower than that of DRV combined with RTV, bioequivalence for the C_{min} was not achieved.[169]

Efficacy in Clinical Trials:

- The AMBER trial enrolled 725 ART-naive participants in a Phase 3 randomized controlled trial that compared the STR DRV/c/TAF/FTC and DRV/c plus TDF/FTC. At 48 weeks, similar virologic suppression rates among participants were achieved in both arms of the study (91% and 88% had HIV RNA < 50 copies/mL, respectively). No treatment-emergent mutations associated with DRV or TAF/TDF resistance were observed in either group. In the DRV plus TAF/FTC arm, fewer participants developed proteinuria. Changes in BMD were also less pronounced among these participants.[52] At 96 weeks, 85% of participants on the STR maintained HIV RNA levels <50 copies/mL.[170]
- In a single-arm trial in which most of the patients were treatment-naive (94%), the coformulated DRV/c 800 mg/150 mg tablet was evaluated in combination with two investigator-selected NRTIs (99% of participants were given TDF/FTC). At week 48, 83% of treatment-naive participants achieved HIV RNA <50 copies/mL; 5% of participants discontinued treatment because of adverse events.[171]

Adverse Effects:

- The most common drug-related adverse events were diarrhea, nausea, fatigue, flatulence, rash, and headache.

Other Factors:

- DRV/c 800 mg/150 mg is available as a coformulated boosted PI or as an STR with TAF/FTC 10 mg/200 mg.

The Panel's Recommendations:

- The Panel recommends DRV/c plus TAF/FTC or TDF/FTC **(AI)** and DRV/c plus ABC/3TC **(BII)** as *Recommended Initial Regimens in Certain Clinical Situation*s.
- DRV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas DRV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

Atazanavir/Ritonavir (ATV/r) or Atazanavir/Cobicistat (ATV/c)

Efficacy in Clinical Trials:

ATV/r plus Two NRTIs versus LPV/r plus Two NRTIs

- The CASTLE study compared once-daily ATV/r (300 mg/100 mg) with twice-daily LPV/r (400 mg/100 mg), each administered in combination with TDF/FTC. In this open-label, noninferiority study, the two regimens showed similar virologic and CD4 responses at 96 weeks.[172]

ATV/r plus Two NRTIs versus EFV plus Two NRTIs

- The ACTG A5202 study compared open-label ATV/r and EFV, each given in combination with placebo-controlled TDF/FTC or ABC/3TC. Efficacy was similar in the ATV/r and EFV groups.[143] In a separate analysis, women assigned to receive ATV/r were found to have a higher risk of virologic failure than women assigned to receive EFV or men assigned to receive ATV/r.[173]

ATV/r plus Two NRTIs versus INSTI plus Two NRTIs

- In a study that compared ATV/r plus TDF/FTC to EVG/c/TDF/FTC, virologic suppression rates through 144 weeks were similar among participants in the two groups.[129] A Phase 3 clinical trial of 575 women evaluated EVG/c plus FTC/TDF versus ATV/r plus FTC/TDF.[15] At week 48, the virologic suppression rate in the EVG/c arm was superior to that in the ATV/r arm. Nineteen women in the PI arm and five women in the INSTI arm discontinued therapy because of an adverse event.
- In a Phase 3 trial, 499 ART-naive women were randomized to receive either ATV/r plus TDF/FTC or DTG/ABC/3TC. At 48 weeks, the rate of virologic suppression (HIV RNA <50 copies/mL) in the DTG arm was noninferior to that in the ATV/r arm, and fewer drug-related adverse events occurred in the DTG arm.[118]

ATV/r plus Two NRTIs versus DRV/r plus Two NRTIs versus RAL plus Two NRTIs

- In ACTG A5257, a significantly higher proportion of patients in the ATV/r arm discontinued randomized treatment because of adverse events, mostly for elevated indirect bilirubin/jaundice or gastrointestinal toxicities. Lipid changes in participants in the ATV/r and DRV/r arms were similar. BMD decreased to a greater extent in participants in the ATV/r and DRV/r arms than in participants in the RAL arm.[13]

ATV/c versus ATV/r plus Two NRTIs

- In the Gilead Study 114, all patients received TDF/FTC and ATV and were randomized to receive either RTV or COBI as PK enhancers. Both RTV and COBI were given as a separate tablet with matching placebos.[174] Through 144 weeks, the percentage of patients who achieved virologic suppression was similar in both study arms. The percentage of adverse events that caused patients to discontinue treatment, and changes in serum creatinine and indirect bilirubin levels were comparable.[175]

Adverse Effects:

- The main adverse effect associated with ATV/c or ATV/r is reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The risk for treatment-limiting indirect hyperbilirubinemia is greatest for patients who carry two UGT1A1 decreased-function alleles.[176]

- Nephrolithiasis,[177-179] nephrotoxicity,[32] and cholelithiasis[180] have also been reported in patients who received ATV.
- Both ATV/c and ATV/r can cause gastrointestinal side effects, including diarrhea.

Other Factors and Considerations:

- ATV/c and ATV/r are dosed once daily and with food.
- ATV requires acidic gastric pH for dissolution. As a result, concomitant use of drugs that raise gastric pH (e.g., antacids, H2 antagonists, and particularly PPIs) may impair absorption of ATV. Table 21a provides recommendations for use of ATV/c or ATV/r with these agents.
- ATV/c and ATV/r are potent CYP3A4 inhibitors and may have significant interactions with other medications that are metabolized through this same pathway (see Drug-Drug Interactions).
- Large observational cohort studies found an association between some PIs (DRV/r, FPV, IDV, and LPV/r) and an increased risk of cardiovascular events; this risk was not seen with ATV.[29-31,34] Another study of an observational cohort of predominantly male participants found a lower rate of cardiovascular events in participants receiving ATV-containing regimens than in participants receiving other regimens.[33] Further study is needed.

The Panel's Recommendations:

- On the basis of clinical trial safety and efficacy data, the Panel classifies ATV/r and ATV/c plus TAF/FTC **(BII)** or TDF/FTC **(BI)** as *Recommended Initial Regimens in Certain Clinical Situations*.
- ATV/c or ATV/r plus ABC/3TC is no longer included in the list of *Recommended Initial Regimens in Certain Clinical Situations*, because it has disadvantages when compared with other regimens in this category. In a randomized trial, when combined with ATV/r, ABC/3TC was less potent than TDF/FTC in people with HIV RNA >100,000 copies/mL;[43] in a separate randomized trial, ATV/r was not as well tolerated as DRV/r.[13]
- ATV/c plus TDF/FTC **is not recommended** for patients with CrCl <70 mL/min, whereas ATV/c plus TAF/FTC **is not recommended** for patients with CrCl <30 mL/min.

Other Antiretroviral Regimens for Initial Therapy When Abacavir, Tenofovir Alafenamide, and Tenofovir Disoproxil Fumarate Cannot Be Used or Are Not Optimal

Most currently recommended ARV regimens consist of two NRTIs plus a third active drug. In some clinical situations, it is preferable to avoid ABC, TAF, and TDF, such as in patients who are HLA-B*5701 positive or at high risk of cardiovascular disease and with significant renal impairment. In this situation, DTC/3TC, which is recommended for most people with HIV, is the preferred option. In addition, several other NRTI-limiting two-drug regimens have been evaluated in clinical studies. Of note, two-drug regimens **should not be used** in people with HBV/HIV coinfection or during pregnancy. Clinicians should refer to HBV/HIV Coinfection for guidance on treatment of patients with HBV infection when TAF or TDF cannot be used as part of the ARV regimen.

Strategies Supported by Evidence from Clinical Trials

Dolutegravir/Lamivudine (DTG/3TC)

Among the two-drug regimens for initial therapy, the combination of DTG/3TC has the most clinical data supporting its use;[4,120,181] therefore, it is recommended over the other two-drug regimens listed below. Clinicians should refer to the INSTI section above for a summary of the data supporting the use of DTG/3TC as initial therapy for ART-naive people with HIV.

The Panel's Recommendation:

- The Panel recommends DTG/3TC as an initial regimen for most people with HIV **(AI)**; as such, this is the preferred regimen when use of ABC, TAF, or TDF is not optimal. DTG/3TC **is not recommended** for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available. Before prescribing DTG/3TC for a person of childbearing potential, review Table 6b for a discussion of important considerations.

Darunavir/Ritonavir plus Lamivudine (DRV/r plus 3TC)

- In the ANDES trial, 145 participants were randomized 1:1 to receive open-label, once-daily dual therapy with DRV/r plus 3TC or triple therapy with DRV/r plus TDF/3TC. This study was conducted in Argentina, and the researchers used an FDC of DRV/r 800 mg/100 mg that is available in that country. The median baseline HIV RNA was 4.5 $\log_{10}$ copies, and 24% of participants had HIV RNA >100,000 copies/mL. At week 48, 93% of the participants in the dual-therapy group and 94% of the participants in the triple-therapy group achieved an HIV RNA <50 copies/mL; dual therapy was noninferior to triple therapy.[39] The rates of virologic suppression among study participants who had pre-therapy HIV RNA levels >100,000 copies/mL were similar in the dual- and triple-therapy groups (91% and 92%, respectively).

The Panel's Recommendation:

- On the basis of results from a small study with a relatively short follow-up period, DRV/r plus 3TC can be considered for use in people who cannot take ABC, TAF, or TDF **(CI)**. Although the ANDES trial supports the use of DRV/r plus 3TC, it is smaller than other trials of NRTI-limiting regimens, and larger studies are warranted.

Darunavir/Ritonavir plus Raltegravir (DRV/r plus RAL)

- In the NEAT/ANRS 143 study, 805 treatment-naive participants were randomized to receive twice-daily RAL or once-daily TDF/FTC, each with DRV/r (800 mg/100 mg once daily). At week 96, DRV/r plus RAL was noninferior to DRV/r plus TDF/FTC based on the primary endpoint of proportion of patients with virologic or clinical failure. Among those with baseline CD4 counts <200 cells/mm^3, however, there were more virologic failures in the two-drug arm; a trend towards more failure was also observed among those with pretreatment HIV RNA ≥100,000 copies/mL.[38] High rates of virologic failure in patients with HIV RNA >100,000 copies/mL were also seen in two smaller studies of DRV/r plus RAL.[182,183]

The Panel's Recommendation:

- On the basis of these study results, the Panel recommends that DRV/r plus RAL be considered for use only in patients with HIV RNA <100,000 copies/mL and CD4 counts >200 cells/mm^3, and only in those patients who cannot take ABC, TAF, or TDF **(CI)**.

A Nucleoside-Limiting Regimen with Insufficient Supporting Data

Darunavir/Ritonavir plus Rilpivirine (DRV/r plus RPV)

- In a single-arm, open-label, pilot study, 36 ART-naive participants without genotypic evidence of resistance to DRV or RPV received DRV/r plus RPV for 48 weeks. Half of the participants (18 of 36) had baseline HIV viral loads >100,000 copies/ml. By week 36, 97% of participants (35 of 36) achieved HIV RNA <50 copies/ml, and by week 48, all achieved viral suppression (HIV RNA <50 copies/ml).[184]

The Panel's Recommendation:

- At this time, the Panel **does not recommend** DRV/r plus RPV given the small sample size of the study described above and the lack of comparative data evaluating DRV/r plus RPV as initial therapy for people with HIV.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 5)

Note: All drugs within an ARV class are listed in alphabetical order.

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Dual-NRTI Regimens	**ABC/3TC**	• Coformulated with DTG • Generic formulations are available for ABC/3TC, ABC, and 3TC.	• May cause life-threatening HSRs in patients who test positive for the HLA-B*5701 allele. As a result, HLA-B*5701 testing is required before use. • In the ACTG 5202 study, patients with baseline HIV RNA ≥100,000 copies/mL showed inferior virologic responses when ABC/3TC was given with EFV or ATV/r as opposed to TDF/FTC. This difference was not seen when ABC/3TC was used in combination with DTG. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies.
	TAF/FTC	• Coformulated with BIC, DRV/c, EVG/c, or RPV • Active against HBV; a recommended dual-NRTI option for patients with HBV/HIV coinfection • Smaller decline in renal function, less proteinuria, and smaller reductions in BMD than TDF/FTC • Approved for patients with eGFR ≥30 mL/min • Can be used in patients with eGFR <30 mL/min and on chronic hemodialysis	• TDF is associated with lower lipid levels than TAF, perhaps because TDF results in higher plasma levels of tenofovir, which lowers lipids. **• Not recommended in pregnancy.**
	TDF/3TC	• Coformulated with DOR • Generic formulations are available for TDF, 3TC, TDF/3TC, and EFV/TDF/3TC. • Long-term clinical experience • Active against HBV	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.
	TDF/FTC	• Coformulated with EFV, EVG/c, and RPV as STRs • Active against HBV; a recommended dual-NRTI option for patients with HIV/HBV coinfection • Better virologic responses than ABC/3TC in patients with baseline viral loads ≥100,000 copies/mL when combined with ATV/r or EFV • Associated with lower lipid levels than ABC or TAF	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency, especially when combined with pharmacologic boosters. • Osteomalacia has been reported as a consequence of proximal tubulopathy. • Decreased BMD has been associated with use of TDF, especially when combined with pharmacologic boosters.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
Single NRTI	**3TC**	• Coformulated with DTG as STR • Avoids potential toxicities associated with TDF, TAF, ABC	• DTG/3TC **is not recommended** for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.
INSTI	**BIC**	• Coformulated with TAF/FTC • Higher barrier to resistance than EVG and RAL • No food requirement	• See Table 6b for considerations related to prescribing an INSTI-based regimen to people of childbearing potential. • Oral absorption of BIC can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • Inhibits tubular secretion of Cr without affecting glomerular function. • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug-drug interactions. • **Should not be used in pregnancy** because of lack of data and coformulation with TAF. • See discussion in text regarding weight gain related to INSTIs.
	DTG	• Higher barrier to resistance than EVG or RAL • Coformulated with ABC/3TC and 3TC • No food requirement • Minimal CYP3A4 interactions • Favorable lipid profile	• Data from Botswana suggest that DTG exposure during conception may be associated with risk of NTDs in the infant (0.3% vs. 0.1% with non-DTG ARV drugs). • See Table 6b for considerations related to prescribing an INSTI-based regimen for a person of childbearing potential. • Oral absorption of DTG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • Inhibits renal tubular secretion of Cr and can increase serum Cr without affecting glomerular function. • UGT1A1 substrate; potential for drug interactions (see Table 21d). • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
INSTI, continued	**EVG/c**	• Coformulated with TDF/FTC or TAF/FTC • Compared with ATV/r, EVG/c causes smaller increases in total and LDL cholesterol. • EVG/c/TAF/FTC can be used in patients on chronic hemodialysis.	• See Table 6b for considerations related to prescribing an INSTI-based regimen for a person of childbearing potential. • EVG/c/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; this regimen should be discontinued if CrCl decreases to <50 mL/min. • COBI is a potent CYP3A4 inhibitor, which can result in **significant interactions** with CYP3A substrates. • Oral absorption of EVG can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Food requirement. • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • **Should not be used in pregnancy** because of low drug exposure. • See discussion in text regarding weight gain related to INSTIs.
	RAL	• Compared to other INSTIs, has longest post-marketing experience • No food requirement • No CYP3A4 interactions • Favorable lipid profile	• See Table 6b for considerations related to prescribing an INSTI-based regimen for a person of childbearing potential. • Has a lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe HSRs (including SJS and TEN) have been reported. • Higher pill burden than other INSTI-based regimens. • No FDC formulation. • Oral absorption of RAL can be reduced by simultaneous administration with drugs containing polyvalent cations (e.g., Al-, Ca-, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 21d. • UGT1A1 substrate; potential for drug interactions (see Table 21d). • Depression and suicidal ideation (rare; usually in patients with pre-existing psychiatric conditions). • See discussion in text regarding weight gain related to INSTIs.
NNRTI	**DOR**	• Coformulated with TDF/3TC • Compared to EFV, fewer CNS side effects • No food requirement • Favorable lipid profile	• Shorter-term clinical experience than with EFV and RPV. • Potential for CYP450 drug interactions (see Tables 21b, 22a and 22b). • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
NNRTI, continued	**EFV**	• EFV 600 mg is coformulated with TDF/FTC and TDF/3TC. • EFV 400 mg is coformulated with TDF/3TC. • EFV 600-mg dose has long-term clinical experience and EFV-based regimens (except for EFV plus ABC/3TC) have well-documented efficacy in patients with high HIV RNA. • EFV 400 mg has fewer CNS side effects than EFV 600 mg. • EFV 600 mg can be given with rifamycin antibiotics (rifampin, rifabutin, or rifapentine).	• Short- and long-term neuropsychiatric (CNS) side effects, including depression and, in some studies, suicidality and catatonia. Late onset ataxia and encephalopathy have also been reported. • Periodic screening for depression and suicidality is recommended in people with HIV who are taking a regimen that includes EFV. • Dyslipidemia • Rash • QTc interval prolongation; consider using an alternative to EFV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes. • Transmitted resistance is more common than with PIs and INSTIs. • Greater risk of resistance at the time of treatment failure than with PIs. • Potential for CYP450 drug interactions (see Tables 21b and 22a). • Should be taken on an empty stomach (food increases drug absorption and CNS toxicities).

	RPV	• Coformulated with TDF/FTC and TAF/FTC
		• RPV/TDF/FTC and RPV/TAF/FTC have smaller pill sizes than other coformulated ARV drugs
		• Compared with EFV:
		  • Fewer CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
			• **Not recommended** in patients with pre-ART HIV RNA >100,000 copies/mL or CD4 counts <200 cells/mm^3 because of higher rate of virologic failure in these patients.
			• Depression and suicidality
			• QTc interval prolongation; consider using an alternative to RPV in patients taking medications with known risk of causing Torsades de Pointes or in those at higher risk of Torsades de Pointes.
			• Rash
			• Transmitted resistance is more common than with PIs and INSTIs.
			• More NNRTI-, TDF-, and 3TC-associated mutations at virologic failure than with regimens that contain EFV and 2 NRTIs.
			• Potential for CYP450 drug interactions (see Tables 21b and 22a).
			• Meal requirement (>390 kcal)
			• Requires acid for adequate absorption.
			  • **Contraindicated** with PPIs.
			  • Use with H2 antagonists or antacids with caution (see Table 21a for detailed dosing information).

PIs	**ATV/c** or **ATV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs. • ATV/c and ATV/r have similar virologic activity and toxicity profiles. • Observational cohort studies have found an association between some PIs (DRV, LPV/r, FPV, IDV) and an increased risk of CV events; this risk has not been seen with ATV. Further study is needed. See text for discussion. • Individual ATV and RTV components are available as generics.	• Commonly causes indirect hyperbilirubinemia, which may manifest as scleral icterus or jaundice. • Food requirement • Absorption depends on food and low gastric pH (see Table 21a for interactions with H2 antagonists, antacids, and PPIs). • Nephrolithiasis, cholelithiasis, nephrotoxicity • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 21a).

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 5 of 5)

ARV Class	ARV Agent(s)	Advantage(s)	Disadvantage(s)
PIs, continued	**ATV/c** Specific considerations	Coformulated tablet	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI **is not recommended** in pregnancy because of low drug levels.
	DRV/c or **DRV/r**	• Higher barrier to resistance than NNRTIs, EVG, and RAL • PI resistance at the time of treatment failure is uncommon with PK-enhanced PIs.	• Skin rash • Food requirement • GI adverse effects • CYP3A4 inhibitors and substrates: potential for drug interactions (see Table 21a). • Increased CV risk reported in one observational cohort study. • Hepatotoxicity has been reported, especially in those with pre-existing liver disease.
	DRV/c Specific considerations	• Coformulated as DRV/c and DRV/c/TAF/FTC	• COBI inhibits active tubular secretion of Cr and can increase serum Cr without affecting renal glomerular function. • Coadministration with TDF **is not recommended** in patients with CrCl <70 mL/min. • COBI (like RTV) is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • COBI **is not recommended** in pregnancy because of low drug levels.

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; Ca = calcium; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; Cr = creatinine; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; eGFR = estimated glomerular filtration rate; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; Mg = magnesium; MI = myocardial infarction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson syndrome; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrosis; UGT = uridine diphosphate glucuronosyltransferase

Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 1 of 2)

ARV Components or Regimens	Reasons for Not Recommending as Initial Therapy
NRTIs	
ABC/3TC/ZDV (Coformulated) As triple-NRTI combination regimen	• Inferior virologic efficacy
ABC/3TC/ZDV plus TDF As quadruple-NRTI combination regimen	• Inferior virologic efficacy
d4T plus 3TC	• Significant toxicities (including lipoatrophy, peripheral neuropathy) and hyperlactatemia (including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis)
ddI plus 3TC (or FTC)	• Inferior virologic efficacy • Limited clinical trial experience in ART-naive patients • ddI toxicities, such as pancreatitis and peripheral neuropathy
ddI plus TDF	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 cell decline • Increased ddI drug exposure and toxicities
ZDV/3TC	• Greater toxicities (including bone marrow suppression, GI toxicities, skeletal muscle myopathy, cardiomyopathy, and mitochondrial toxicities such as lipoatrophy, lactic acidosis, and hepatic steatosis) than recommended NRTIs
NNRTIs	
DLV	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ETR	• Insufficient data in ART-naive patients
NVP	• Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including SJS and TEN) • When compared to EFV, NVP did not meet noninferiority criteria
PIs	
ATV (Unboosted)	• Less potent than boosted ATV
DRV (Unboosted)	• Use without RTV or COBI has not been studied
FPV (Unboosted) or **FPV/r**	• Virologic failure with unboosted FPV-based regimen may result in selection of mutations that confer resistance to FPV and DRV • Less clinical trial data for FPV/r than for other RTV-boosted PIs
IDV (Unboosted)	• Inconvenient dosing (3 times daily with meal restrictions) • Fluid requirement • IDV toxicities, such as nephrolithiasis and crystalluria
IDV/r	• Fluid requirement • IDV toxicities, such as nephrolithiasis and crystalluria
LPV/r	• Higher pill burden than other PI-based regimens • Higher RTV dose than other PI-based regimens • GI intolerance
NFV	• Inferior virologic efficacy • Diarrhea
RTV as sole PI	• High pill burden • GI intolerance • Metabolic toxicity

Table 10. Antiretroviral Components or Regimens Not Recommended as Initial Therapy (page 2 of 2)

ARV Components or Regimens	Reasons for Not Recommending as Initial Therapy
PIs, continued	
SQV (Unboosted)	• Inadequate bioavailability • Inferior virologic efficacy
SQV/r	• High pill burden • Can cause QT and PR prolongation; requires pretreatment and follow-up ECG
TPV/r	• Inferior virologic efficacy • Higher rate of adverse events than other RTV-boosted PIs • Higher dose of RTV required for boosting than other RTV-boosted PIs
Entry Inhibitors	
T-20 Fusion Inhibitor	• Only studied in patients with virologic failure • Twice-daily subcutaneous injections • High rate of injection site reactions
IBA CD4 Post-Attachment Inhibitor	• Only studied in a very small number of patients with virologic failure • Requires IV therapy • High cost
MVC CCR5 Antagonist	• Requires testing for CCR5 tropism before initiation of therapy • No virologic benefit when compared with other recommended regimens • Requires twice-daily dosing

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; ECG = electrocardiogram; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RTV = ritonavir; SJS = Stevens Johnson Syndrome; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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